University of Alberta

An Investigation of Zinc Exposure and Metal Fume Fever in Chinese Foundry Workers

by

Christopher John Martin ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

in

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The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled "An Investigation of Zinc Exposure and Metal Fume Fever in Chinese Foundry Workers" submitted by Christopher John Martin in partial fulfillment of the requirements for the degree of Masters of Science in Medical Sciences - Public Health Sciences.

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Abstract

Metal fume fever is a self-limited but very uncomfortable condition closely resembling influenza, most frequently associated with inhalational exposure to zinc oxide fumes. Numerous case reports indicate that metal fume fever can be accompanied by changes in pulmonary function and the chest radiograph. However, the nature and timing of these changes are not well understood. Furthermore, very little is known regarding the toxicokinetics of inhaled zinc, making the interpretation of zinc measurements in serum and urine problematic.

A systematic investigation of 20 workers exposed to high levels of zinc oxide in a foundry in Baiyin, Peoples' Republic of China was undertaken to investigate these two areas. Clinical investigations consisted of serial examinations by a physician, chest radiographs and spirometry. Exposure assessment consisted of the measurement of zinc in serum, a cross shift urine collection, and personal air samples.

No cases of metal fume fever were observed during the study period despite exposures to as high as 36.3 mg/m^3 over less than 4 hours. In addition, no radiographic or functional changes were noted. Serum zinc levels of all workers were within the reference range, however, elevations were noted in urinary zinc levels. Statistical analysis showed a significant association ($p=0.04$) between exposure to zinc and urine zinc. These results provide exposure measurements for zinc at which workers demonstrate tolerance to the development of metal fume fever. Furthermore, they suggest that urine may be the preferred matrix for the biological monitoring of zinc as well as in suspected cases of metal fume fever.

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1. LITERATURE REVIEW[1]

1.1 Clinical Features of Metal Fume Fever

Metal fume fever is a very uncomfortable condition closely resembling influenza, most frequently associated with exposure to zinc oxide. The condition is common among workers and goes by many names, including "Monday morning syndrome", "foundry fever", "the smothers", "spelter shakes", "welder's ague", and "brass chills". It typically begins four to six hours after exposure with symptoms resolving after 24 to 48 hours without specific treatment. One peculiar feature of metal fume fever is the phenomenon of tachyphylaxis or tolerance in which workers are asymptomatic with repeated exposure. This tolerance is gained and lost quite rapidly. Tachyphylaxis has been demonstrated to occur experimentally in humans after a single high level exposure for eight minutes (Drinker et al. II, 1927). Workers exposed to zinc oxide fume also know that the tolerance is lost after two days without exposure, accounting for the term "Monday morning syndrome."

Blanc and Boushey (1993) reviewed all case reports as well as cohort and experimental studies on metal fume fever available for the preceding 80 years and summarized the frequency of symptoms as follows: chills (98%), headache (69%), myalgia (61%), cough (59%), dyspnea (38%), and nausea (20%). Prior to the development of fever, a prodromal stage is recognised which can include additional symptoms of throat irritation (83%) and a sweet or metallic taste in the mouth (80%) as well as headache (66%) and cough (42%) (Blanc and Boushey, 1993). In human experiments, these prodromal symptoms have been reported within minutes of a single high level exposure (Sturgis et al., 1927).

The fever in patients with metal fume fever is usually in the range of 38 to 39 °C (Blanc and Boushey, 1993). Another finding is a marked peripheral leukocytosis with a predominance of polymorphonucleocytes. White blood cell

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1. A version of this chapter has been published. Martin CJ, Guidotti TL, and Langård S, (1997). Respiratory hazards of welding. Clin Pulm Med 4(4): 194-204.

counts of between 9.0 and to 36.5 x 10^9 cells / L have been reported (Blanc and Boushey, 1993).

Those at risk of developing metal fume fever include individuals cutting or welding galvanized steel, zinc or brass foundry workers, and zinc sprayers.

1.2 Selected Historical Review

A description suggestive of metal fume fever can be found in a work by Patissier (1822), quoted in Drinker (1922) who described "a colic often accompanied by *des douleurs terribles*" produced by "the oxidized vapours of copper and zinc". However, the first complete, unequivocal description of this entity is usually attributed to Thackrah (1832) who lists the typical symptoms of metal fume fever in workers involved in brass manufacture. He also correctly singled out zinc oxide as the causative agent.

However, the first article to use the term metal fume fever was published by Koelsch (1923). In this document, the Bavarian Inspector of Factories was responding to an article by Philip Drinker of the Harvard Medical School that had been published seven months earlier (Drinker, 1922). Drinker had exhaustively reviewed the literature on metal fume fever (which he referred to as brass founders' ague) and concluded that the oxides of zinc were the only possible cause of the disease based on its physical and chemical properties. He described the symptoms of the ague as consisting of dyspnea, fever, chills, fatigue, sweating, and occasional vomiting occurring several hours after exposure to freshly formed zinc oxide. The course was invariably benign and self-limited with the worker returning to work the next day.

Koelsch (1923) had noted virtually identical symptoms among ten workers at a copper rolling mill exposed to "red-hot glowing ingots of pure copper." He therefore argued that copper could cause an illness similar to that described by Drinker. Without explicitly introducing the term in the body of his article, he entitled his work "Metal-Fume Fever", the first use of this phrase. However, he went further than adding copper to the list of causes of this entity. After

reviewing additional case reports and animal studies, he concluded that "similar symptoms may occur from [the] inhalation of the vapour of all heavy metals." Some of the case reports he described included exposure to such well-known causes of toxic pneumonitis as nickel carbonyl and included "fresh dyspneic symptoms, ... coughing with blood stained expectoration" 12 to 36 hours after the initial exposure. Indeed Koelsch commented on "the extraordinary resemblance between the symptoms of metal [fume] fever and anaphylactic shock". Hence, the purist might argue that the term metal fume fever, in its original usage, refers to the adverse health effects of breathing any metal fume. Most authorities today would not refer to anything other than a benign flu-like illness lasting no longer than 48 hours as metal fume fever, however, the confusion surrounding the term metal fume fever persists, as will be discussed further under section 5.1 "Distinguishing metal fume fever from toxic pneumonitis".

Much of our current understanding of metal fume fever is based on a series of four human experiments that Drinker and his colleagues went on to publish in 1927 (Sturgis et al., 1927; Drinker et al. II, 1927; Drinker et al. III, 1927; Drinker et al. IV, 1927). In the first experiment, they reproduced metal fume fever in two healthy human subjects breathing zinc oxide at an estimated concentration of 600 mg/m^3 for 5 and 12 minutes respectively (Sturgis et al., 1927). Within 30 minutes, they developed symptoms of metal fume fever, which resolved within 48 hours. Other typical features were noted, such as a fever and peripheral leukocytosis, both of which peaked at about 12 hours after exposure. The second experiment served to formally document the acquired tolerance to zinc oxide, which the investigators had suspected from personal experience (Drinker et al. II, 1927). The same two subjects were exposed to high levels of zinc oxide on two successive days. After the second inhalation, both subjects experienced a much milder course with fewer symptoms and a lower rise in temperature and white cell count.

The group was also able to reproduce metal fume fever, albeit much less readily, through the inhalation of magnesium oxide in the third experiment (Drinker et al. III, 1927). In the final set of experiments, they attempted to

determine the threshold dose that would produce metal fume fever through a series of 27 inhalations in 10 different subjects (Drinker et al. IV, 1927). Unfortunately, due to technical constraints at that time, the concentrations in each of the inhalations varied widely. They calculated a threshold limit of 15 mg/m^3 which they felt was safe over 8 hours. In this last paper, the authors also addressed two other areas. In terms of prevention, they advocated local exhaust ventilation and respiratory protection for brief high-level exposures. They also concluded that inhaled zinc did not cause chronic damage.

Following Drinker's work, there was very little research conducted on metal fume fever for almost 60 years.

1.3 Incidence of Metal Fume Fever

1092 cases of metal fume fever were reported in 1994 to poison control centres in the United States (Litowitz, 1995). Blanc and Boushey (1993), extrapolating from the "Doctors' First Report" system of California, derive a figure of 1500-2500 cases annually in the USA. However, these figures underestimate considerably the incidence of metal fume fever.

The Occupational Safety and Health Administration 15 minute short term exposure limit (STEL) for zinc oxide is 10 mg/m^3 while the time-weighted average permissible exposure limit (TWA PEL) is 5 mg/m^3 (OSHA, 1989). The STEL can readily be exceeded without exceeding the PEL, since the latter measurement is averaged over 8 hours. Metal fume fever has experimentally been triggered by short-term high exposures (Sturgis et al., 1927). Therefore, this condition could occur in workplaces with brief high levels of zinc that nevertheless comply with the PEL. Animal studies have demonstrated pulmonary changes with exposure to levels of 5 mg/m^3 for 2 to 3 hours (Gordon et al., 1992). In a recent study, Fine et al. (1997) produced fever and symptoms in ten of thirteen naïve subjects inhaling zinc oxide at 5 mg/m^3 for 2 hours. Exposure to 2.5 mg/m^3 caused a mild fever without other symptoms in nine of the subjects. Fine et al. (1997) further

cite unpublished work from their laboratory demonstrating lung injury in animals exposed to as little as 1 mg/m^3 for 3 hours.

Taken together, these data indicate that metal fume fever may be quite a frequent occurrence in the work place and cast doubt on the protective value of the current TLV of 5 mg/m^3. Because of their familiarity with this disease - both its benign course and the development of tolerance - many workers do not seek medical attention for the condition, leading to substantial under-reporting.

1.4 Pathophysiology of Metal Fume Fever

Metal fume fever is a poorly understood entity. It is clinically indistinguishable from several other disorders which result from the inhalation of a diverse array of agents including organic dust toxic syndrome caused by various bioaerosols and polymer fume fever caused by the pyrolysis products of tetrafluoroethylene resins (Teflon®). All of these conditions also share the phenomenon of tachyphylaxis (Rask-Anderson, 1996). Because of this striking similarity, the term inhalation fever has been advocated to encompass these conditions (Rask-Anderson, 1996).

Several pathophysiological models have been proposed for metal fume fever. A speculative work by McCord (1960), which is still frequently cited (See ATSDR, 1994), proposed that metal fume fever was an immunological disease. The inhaled zinc oxide was proposed to damage the respiratory tract, producing a metal protein conjugate which served as an antigen for an allergic response. Tachyphylaxis was accounted for by the later formation of anti-antibodies to this conjugate. It is well known that metal fume fever can develop upon first exposure to zinc oxide (Sturgis et al., 1927), ruling out any sort of antibody mediated mechanism. McCord (1960) was aware of this fact and stated that the initial episode could be caused by histamine release with subsequent episodes accounted for by the formation of antibodies. An improved knowledge in immunology together with recent findings from bronchoalveolar lavage studies has now rendered this hypothesis untenable.

A more plausible explanation is based on cytokines (Blanc et al., 1993). In this model, the inhaled zinc oxide causes pulmonary macrophages to synthesize and release cytokines. The released cytokine(s) would then initiate a cascade of mediators leading to the host of systemic flu-like symptoms. Tumour necrosis factor alpha (TNF- α), interleukin-6 (IL-6) and interleukin-8 (IL-8) have all been found in elevated levels in the supernatant of bronchoalveolar lavage fluid obtained at 3, 8, or 22 hours post exposure from 26 individuals subjected to welding fume challenges over 15 to 30 minutes (Blanc et al., 1993). The mean cumulative exposure to zinc oxide in this study was 2100 mg min / m^3, which translates into mean air concentrations of between 70 to 140 mg/m^3. In this study, the authors do not discuss the symptoms in those exposed to the welding fume challenge. However, the results of investigations on 14 of the 26 subjects were also reported in earlier report (Blanc et al., 1991). In this paper, the authors state that four of the participants with the heaviest exposures had symptoms of metal fume fever (myalgias) prior to bronchoscopy, with two of the four experiencing fevers greater than 38 °C (Blanc et al., 1991). Four subjects in the early bronchoscopy group also experienced myalgias or fever. However, these symptoms occurred after bronchoscopy, which in itself is known to cause such symptoms (Crystal et al., 1985).

Moreover, the elevation in cytokines occurred in a dose-dependent fashion. According to the investigators, the key cytokine in initiating this process may be TNF-α since it showed the earliest elevation at 3 hours post exposure (Blanc et al., 1993). Serum levels of IL-6, IL-8, and TNF-α were not found to be elevated in this study.

This impressive pulmonary response was observed even in the lavage fluid of those exposed subjects without any symptoms of metal fume fever (Blanc et al., 1991). This finding led the authors to conclude that even a "subclinical" exposure to zinc oxide could result in a significant inflammatory response (Blanc et al., 1993).

A recent study by Fine et al. (1997) investigating thirteen naïve subjects exposed to 5 and 2.5 mg/m^3 for 2 hours on separate days presents somewhat

conflicting data. A control exposure to furnace gas composed of 97% room air and 3% argon was included in the study. Twelve subjects completed the protocol, one dropped out after two exposures for unspecified reasons. From the 2.5 mg/m^3 exposure, nine subjects experienced a mild fever (reported as a mean increase of 1.2 ± 0.3 °F equivalent to 0.7 ± 0.2 °C) without other associated symptoms. From the exposure to 5 mg/m^3, an increase in mean temperature of 1.4 ± 0.3 °F (0.8 ± 0.2 °C) was observed together with symptoms in eleven of the twelve subjects. The air exposure resulted in a 0.6 ± 0.5 °F (0.3 ± 0.3 °C) increase in mean temperature. These investigators also measured plasma IL-6 and TNF-α levels. In contrast to the studies by Blanc et al. (1993), statistically significant increases in mean plasma IL-6 levels were observed following the 2.5 mg/m^3 and 5 mg/m^3 inhalations in comparison to the air exposure. The magnitude of this rise in IL-6, measured at 3 and 6 hours after exposure, was very similar for both exposures. No trends were apparent for the measurements of circulating TNF-α. However, fewer measurements were made (n = 6 to 10) because of "limited specimen availability" (Fine et al., 1997). The authors state that the discrepancy in findings between their study and those of Blanc et al. (1993) may be attributable to the testing of more subjects at shorter intervals.

In summary, there is mounting, yet somewhat divergent, evidence implicating cytokines in the pathophysiology of metal fume fever. The wide variety of cytokines produced in the lung, many with multiple functions, has led Fine et al. (1997) to conclude that "it appears likely that complex interactions of cytokines, rather than a simple chain reaction, participate in pulmonary/systemic syndromes such as metal fume fever."

1.5 Causes of Metal Fume Fever

While there is no dispute that exposure to zinc oxide fumes (usually in the context of welding galvanized steel or founding zinc) causes metal fume fever, many authors also refer to a long list of other metals as putative causes, variously implicating the oxides of copper, magnesium, manganese, selenium,

silver, aluminium, nickel, cadmium, mercury, chromium, iron, tin and antimony (Hunter, 1978; Zakhari and Andersen, 1981; Piscator, 1976). Blanc and Boushey (1993) question the basis for ascribing metal fume fever to many of these agents. They take a relatively conservative view, stating that only the oxides of zinc, magnesium, and copper are proven causes. The evidence for magnesium is based on the third experiment by Drinker's group in which metal fume fever was reproduced, albeit much less readily, in subjects inhaling magnesium oxide (Drinker et al. III,1927).

However, a recent study by Kuschner et al. (1997) casts serious doubt on the ability of magnesium to provoke metal fume fever. Six subjects underwent BAL, pulmomary function testing (PFT), and peripheral CBC determinations following 18 to 20 hours after exposure to magnesium oxide fumes with a mean cumulative exposure of 4 138 ± 2 163 mg min/m^3. No symptoms were observed following the magnesium oxide exposure and no significant differences between control and post exposure results were noted for peripheral blood neutrophil counts, pulmonary function, or BAL inflammatory cell counts, levels of IL-1, IL-6, IL-8, or TNF (Kuschner et al., 1997).

The evidence for copper is derived from an accumulation of reports, with no single compelling report (Blanc and Boushey, 1993). Mixed exposures in many occupational settings render tentative any conclusions about a causative role for single agents on the basis of a case report.

1.6 Pulmonary Involvement in Metal Fume Fever

Many authors state that the chest radiograph is typically normal in metal fume fever (Barnhart and Rosenstock, 1984; Blanc and Boushey, 1993). However, an accumulation of case reports together with experimental evidence indicate that both radiographic and functional changes may occur quite frequently in metal fume fever.

One of the largest case series of metal fume fever, which included 43 cases reported from workers in the Gdansk shipyard in Poland, was published in

1973 (Jaremin, 1973). In the 39 patients who had chest radiographs taken, five showed "fine-spotted, striped or faint round-shaped shadows". A case report of a commercial zinc sprayer who developed a particularly severe case of metal fume fever with hypoxia appeared in the British literature in 1987 (Langham Brown, 1987). His chest radiograph, taken at an unspecified time after exposure showed a florid micronodular infiltrate that cleared after 4 days. Noel and Ruthman (1988), in reporting the results of serum zinc measurements in 2 cases of metal fume fever, mention that in the one case in which a chest radiograph was taken, it showed "vascular congestion with a normal heart size." Malo et al. (1990) described a case with typical features of metal fume fever (fever, malaise, and dyspnea) following exposure to zinc oxide fumes. However, since the patient also had transient diffuse nodular infiltrates on chest radiograph at presentation with reductions in FEV_1 and FVC observed when he was exposed to his usual work conditions for 1 hour, the authors speculated that an acute lung reaction, distinct from metal fume fever, was occurring. Ambient levels of zinc oxide were not measured nor was the timing of the abnormal chest radiograph in relation to exposure mentioned.

Nemery and Demdts (1991) responded to the description by Malo et al. (1990) by providing an additional case report of a man with similar symptoms but who also demonstrated a decrease in self-recorded peak flows which reached a nadir approximately 24 hours after the start of exposure. His chest radiograph was normal but, as the authors point out, he was not seen during the time of illness. Nemery and Demdts (1991), after reviewing Drinker's work, correctly point out that decreases in vital capacity occurred in both of Drinker's subjects 8 to 12 hours after exposure. Although there were no radiographic changes in Drinker's subjects, as Nemery and Demedts (1991) observed, the chest radiographs were taken at 3.5 hours and again at 8 days after exposure and may therefore have missed the transient changes that others have described. Apparently overlooked in the discussion is a follow-up article by Drinker and colleagues, addressing the issue of the long-term effects of zinc oxide, offering

the following statement regarding the radiographic examinations of one of the two subjects (Drinker et al. IV, 1927) :

"The first of these examinations was made in July, 1926, another on Oct. 27, 1926, during an attack of the fever, and the third eight days later. The first and last examinations were negative; *the second showed transient effects which had disappeared by the time of the third examination.*" (Italics added.)

Unfortunately, the timing of the second abnormal chest radiograph in relation to exposure is not mentioned.

Following the pioneering work by Drinker in the 1920s, there was no further attempt to reproduce metal fume fever in humans until 1987. At that time, Vogelmeier et al. (1987) reported the results of investigations on a man particularly prone to the development of metal fume fever with recurrent episodes whenever he welded zinc-containing materials. They performed two controlled exposures in which the subject welded on a zinc-coated tube for one hour. External levels of zinc generated were not reported. Pulmonary function testing was performed every 1-2 hours for 7 hours after the exposure and again at 24 hours. A CBC was performed at 7 and 24 hours. Bronchoalveolar lavage (BAL) was performed at 24 hours after the challenge and following a 7 week period without exposure to zinc oxide. Chest radiographs taken when the man was asymptomatic and at an unspecified interval following the first exposure were normal.

Pulmonary function testing revealed a 40% decrease from baseline in inspiratory vital capacity (IVC) and DL_{CO}. The depression in IVC was maximal at 6 hours while that of DL_{CO} occurred at 4 hours. The arterial oxygen partial pressure (P_a0_2) dropped by 9 mmHG. Similar results were found following the second exposure. In both cases, the results normalised within 24 hours, with the exception of a mild decrease in DL_{CO}. The BAL at 24 hours revealed a marked leukocytosis ten times the normal value (94×10^6 total cell count) with an increase in polymorphonuclear (PMN) leukocytes.

The study by Blanc et al. (1991) on 14 subjects exposed to a welding fume challenge for 15 to 30 minutes included pulmonary function testing (PFT),

BAL, and CBC. The authors provide a mean cumulative exposure to zinc oxide of 2 300 mg min/m^3 which translates into a mean air concentration of between approximately 77 to 150 mg/m^3. Chest radiographs were not included in the protocol. In contrast to the results of Vogelmeier et al.'s (1987) work, there was little change in pulmonary function apart from a mean 7% reduction in DL_{CO}. The BAL findings were similar to those reported by Vogelmeier's group with a marked PMN leukocytosis in all 14 subjects. Similarly, a doubling in peripheral PMN leukocytes was noted. An extension of this study, which included BAL on an additional nine subjects, confirmed these findings (Blanc et al., 1993).

Gordon et al. (1992) administered a dose of 5 mg/m^3 of zinc oxide to four human subjects for 2 hours. The authors considered all four subjects to have developed metal fume fever since they each experienced at least one of the classic symptoms. However, one subject developed chest tightness and a dry throat and the other experienced "headache, irritated throat, sputum" (Gordon et al., 1992). Temperature measurements or peripheral white cell counts to support a diagnosis of metal fume fever were not included in the study. No changes were noted in spirometry, which was performed immediately prior to and after the exposure. As in Drinker's study (Sturgis et al., 1927), this timing may have been too early to identify the changes that others have noted. However, self-administered peak flow measurements at 0, 4, 8, and 24 hours after exposure showed no change.

Thus, there is ample evidence from case reports and limited experimental studies that radiographic and functional changes can accompany metal fume fever. Such changes are generally under-appreciated, and they are also not usually systematically sought. Accordingly, the nature of these changes is not well understood with patterns of both an obstructive and restrictive nature being reported.

1.7 Toxicokinetics of Inhaled Zinc

Another common misconception concerning metal fume fever highlighted by Blanc and Boushey (1993) is that it can only be caused by freshly formed fumes of zinc oxide. Two members of Drinker's group produced metal fume fever in themselves following inhalation of a commercially available finely ground zinc dust with an estimated particle size of 0.15 μm (Drinker et al. IV, 1927). Two cases have also been reported in workers using automatic steel wire buffer machines to clean metal water tanks (Rohrs, 1957).

Zinc oxide must be present as ultrafine particles in order to be effectively delivered to the alveoli. Shortly after generation, these particles flocculate, forming much larger chains that are not effectively delivered to the alveoli. Sufficiently small particles are far more readily generated by the high temperatures of welding or foundry work than by most physical means. Thus, the overwhelming preponderance of cases of metal fume fever in response to exposure to zinc oxide fumes simply reflects the physical constraints governing the route of exposure.

Very little is known about the toxicokinetics of zinc following inhalational exposure. As Blanc and Boushey (1993) point out, the lung plays a key role in initiating metal fume fever and does not merely serve as the route of exposure since the symptoms of metal fume fever are not elicited by the ingestion or intravenous administration of toxic levels of zinc. Studies in rats have indicated that zinc oxide is rapidly cleared from the lung, with an estimated half-life of 14 hours following intratracheal instillation (Hirano et al., 1989).

In the same study, Hirano et al. (1989) also demonstrated a dose dependent induction of the low molecular weight protein metallothionein in the lung. The chronology of this induction is highly suggestive of a role for metallothionein in the development of tachyphylaxis in metal fume fever. Peak metallothionein concentrations were noted 2 days after zinc oxide exposure and returned to control levels after 3 to 5 days, corresponding closely to the time course of tachyphylaxis in metal fume fever. A role for metallothionein in the

development of a different type of tolerance has been postulated in other settings. Leber and Miya (1976) showed increased tolerance to subcutaneous injection of cadmium in mice that had been pre-treated with either cadmium or zinc and implicated hepatic metallothionein in this process. The major difficulty with invoking a role for metallothionein in the tolerance of metal fume fever lies in the observation that tachyphylaxis has also been unequivocally demonstrated in other inhalation fevers, such as polymer fume fever (Nuttal et al., 1964). Polymer fume fever is caused by the pyrolysis products of polytetrafluoroethylene and does not involve metals.

Information regarding the metabolism of zinc relates to the gastrointestinal, not inhalational, exposure route. The peripheral utilization of zinc has not been characterized and no storage site in the body has been identified (Prasad, 1993). Nevertheless, zinc is ubiquitous in the body and is a cofactor in over 200 enzymes (ATSDR, 1994). A role for metallothionein in the intracellular regulation of zinc, copper, cadmium and several other metals has also been proposed (Prasad, 1993). No estimates of the half-life of zinc in circulation were identified.

Most zinc in the circulation is present in erythrocytes, of which 87% is bound to the enzyme carbonic anhydrase (Ohno et al., 1985). Serum zinc levels may be as much as 16% higher than plasma, which has been attributed to a combination of zinc released from platelets during coagulation and invisible erythrocyte hemolysis (Prasad, 1993). The plasma fraction is thought to represent the metabolically active pool for zinc (Cousins, 1985). Transferrin, α-2-macroglobulin, and albumin have all been proposed as transport proteins for circulating zinc (Prasad, 1993) with approximately two-thirds of the zinc in plasma bound in a loosely and freely exchangeable manner to albumin (Cousins, 1985). For these reasons, zinc is usually measured in serum or plasma. A widely accepted reference range for zinc in plasma is 70 to 150 μg/dL or 10.7 to 22.9 μmol/L (Milne, 1994).

Zinc is excreted mainly via feces (5 to 10 mg/day) as well as urine (200 to 600 μg/day) (Prasad, 1993). The rate of both of these routes of excretion varies

according to zinc nutritional status. Studies in dogs have provided evidence of both proximal secretion and distal reabsorption of zinc in the nephron (Abu-Hamdan et al., 1981). As with other trace elements, urinary zinc measurements are ideally made on 24 hour collections to account for variations in urine output. A widely accepted reference for zinc in urine is 0.15 to 1.20 mg/day or 2.3 to 18.4 μmol/day (Milne, 1994).

2. OBJECTIVES

From the literature review, two broad areas were identified as being in need of further research.

The first relates to the clinical features of metal fume fever. The present study sought to describe the changes that occurred in metal fume fever with respect to lung function, the chest radiograph, and the clinical examination.

The second area relates to the toxicokinetics of zinc exposure. Specifically, what zinc exposure levels could result in metal fume fever as well as the relationship between inhalational exposure to zinc and the levels measured in serum and urine.

An investigation of a prospective nature was selected to permit a precise correlation between the development of metal fume fever with measured exposure levels and to provide a complete temporal description of the natural history of this condition.

In order to observe sufficient cases of metal fume fever, a group of workers from a foundry in central China with high exposure to zinc were chosen for investigation.

3. METHODOLOGY

Two members of the Department of Public Health Sciences, University of Alberta (X. Chris Le, Christopher Martin) travelled to the city of Baiyin in Gansu Province of the Peoples' Republic of China. Two colleagues in China, Dr. Chaoke Liang of the Chinese Academy of Preventive Medicine and Dr. Baoshan Yuan of Lanzhou Medical College assisted in coordinating the study. The actual protocol was administered by members of the Baiyin Labour Institute with assistance from Drs. Le and Martin.

Financial support for the study was provided by the Occupational Health Program at the University of Alberta, which has had contact with the Chinese Academy of Preventive Medicine since 1987.

3.1 Background on the Study Site

The study was carried out on workers in a zinc foundry within the Northwest Lead/Zinc Foundry of Baiyin Corporation, in the industrialized city of Baiyin, about 200 km northwest of the city of Lanzhou (Figure 1). The industry in this area is based on the refining of ore from a local mine which contains copper, lead, and zinc. In the particular foundry studied, zinc ingots from an adjacent smelter are melted and undergo a final refining step.

Operation of this foundry began in 1986 and annual production is estimated to be approximately 100 000 tons as solid zinc ingots with an additional 5 000 tons of zinc powder. The building housing the foundry is approximately 250 meters long, 70 meters wide, and 50 meters high (Figure 2). Zinc cathode sheets from an adjacent smelter are melted down in six furnaces. One is a reflection furnace generating 5 tons of zinc powder per shift. The remaining five electrical furnaces all generate solid zinc ingots. Three are 40 ton units with a production speed of 25 to 27 tons per shift each. Two are 20 ton units operating at about half the production speed of the larger furnaces, or 12 to 14 tons per shift.

Figure 1. Location of Study Site in China

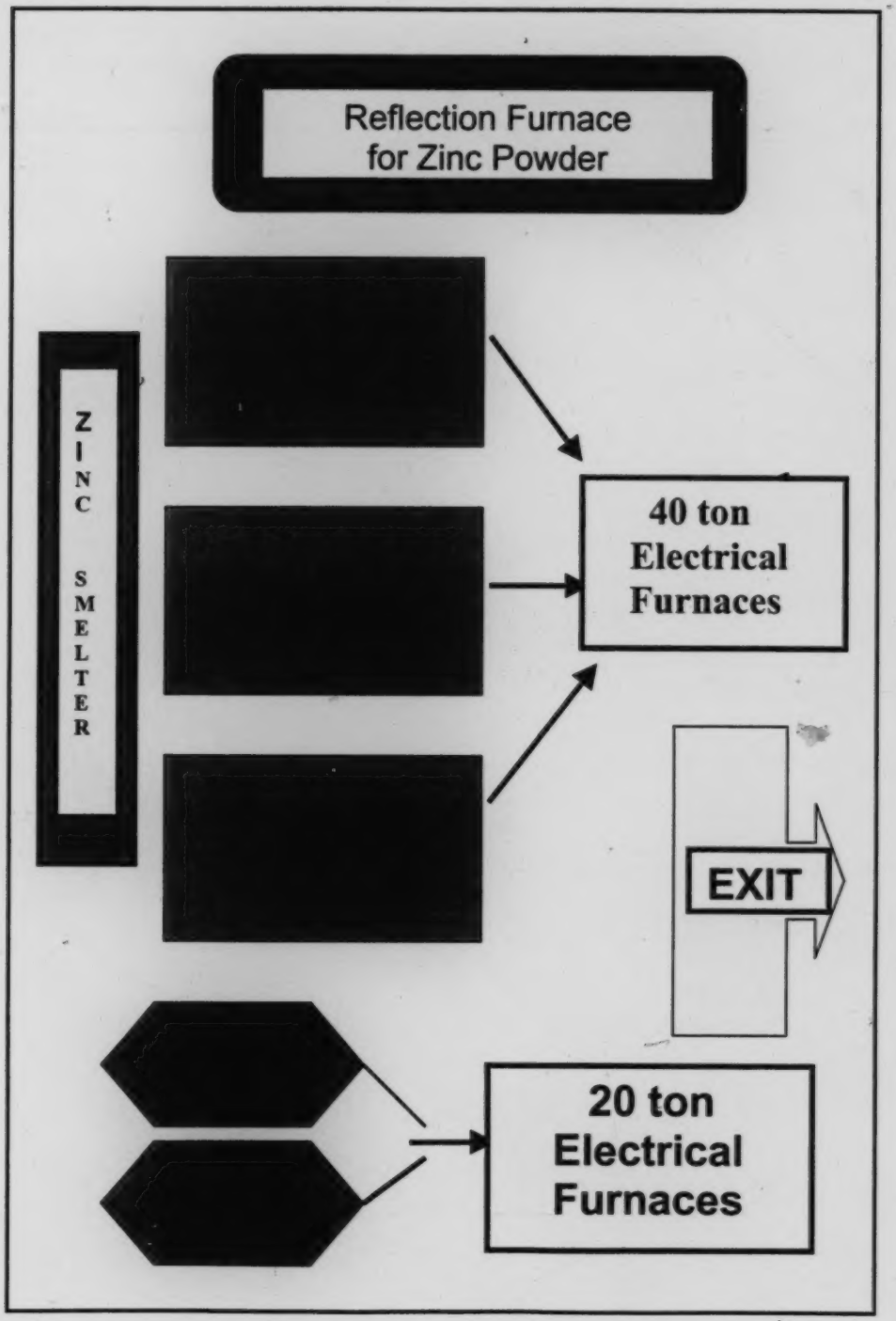

Figure 2: Simplified diagram of Zinc Foundry

Two cranes fixed to the ceiling are used, one to transport zinc sheets to the furnaces, the other totransport and stack the cooling ingots.

The casting method does not involve sand-based moulds. Molten zinc is poured into a metallic mould which is cooled by water and reused.

The foundry is in continuous operation 340 days a year with 25 days a year scheduled for maintenance. Work is divided into three 8-hour shifts beginning at 8 AM. There are four groups of workers who work rotating shifts.

3.2 Ethics Approval

Ethics approval for the study was obtained from the Research Ethics Board of the Faculty of Medicine and Oral Health Sciences, University of Alberta prior to the study. The Research Ethics Board directed the investigators to attempt to identify an equivalent body in China for local ethical approval. However, despite working through colleagues in China, no such body was located. Instead, the workers were represented by members of the Baiyin Labour Institute as well as their supervisor, who was a participant in the study. The protocol was explained to all workers through an information sheet translated into Chinese (Appendix 1). Written informed consent was obtained for each worker from the group's supervisor who signed each worker's consent form on their behalf.

The protocol was modified from that submitted to the Research Ethics Board. The timing of the investigations was altered to minimize disruption to the workplace. The number of chest radiographs was reduced from four to two.

3.3 Study Subjects

All workers studied were performing an 8 AM to 4 PM shift. They were examined before the start of the shift, in the middle of the shift, after the shift, and 24 hours post-shift. This timing was chosen to minimize disruption in the workplace. Four subjects were studied daily on five consecutive days. For the

purposes of the protocol, each subject was designated with a number from 1 to 20.

The workers included in the study were chosen by an on site safety supervisor without any attempt on the part of the investigators to systematically sample the workforce. Later in the study, the investigators selected a few workers for participation who were suspected to have a high level exposure to zinc oxide fumes, based on a tour of the foundry. Since the aim of the study was to observe cases of metal fume fever, the workers who participated were not representative of the workforce as a whole. Indeed, the intention was to select those workers with greater than average exposure to zinc fumes.

In general, there was no clear delineation of duties between the workers. Rather, each worker performed a variety of tasks in the course of the shift including: adding zinc plates to the furnace, mixing and removing residues from the furnace, removing cooled zinc ingots from the moulds, packing zinc powder from the 5 ton furnace, removing zinc oxide film from the molten zinc, operating the cranes, safety patrolling, and performing miscellaneous repairs.

The protocol was intended to be administered to both a larger number of subjects as well as being restricted to workers who had not worked recently. However, as the workers do not have holidays or weekends off work, they are seldom away from the work site for more than 48 hours. Finally, the investigators were only permitted to study twenty workers over five days.

3.4 Investigations

Investigations were performed in two broad areas: a clinical assessment and an exposure assessment which are summarized in Table 1.

3.4.1 Clinical Assessment

The clinical assessment consisted of an interview and examination performed by a physician, chest radiographs, and spirometry.

3.4.1.1 Medical Interview and Examination

All subjects were interviewed and examined by a Chinese physician with minimal supervision by the Canadian investigators. A questionnaire (Appendix 2) was administered which focussed on the respiratory health of each worker, occupational history, and previous episodes of metal fume fever.

Table 1: Summary of Methodology

Pre-Shift	Mid-Shift	Post-Shift	24 Hours Post-Shift
Clinical Assessment			
Baseline medical interview and physical examination	Medical interview and physical examination	Medical interview and physical examination	Medical interview and physical examination
Spirometry	Spirometry	Spirometry	Spirometry
Chest radiograph		Chest radiograph	
Exposure Assessment			
Timed urine collection	→		
Personal air sampling	→		
		Serum and whole blood collection	

A history of metal fume fever was elicited by asking the question: " Have you ever had attacks of fever and chills in relation to your work that do not seem to be caused by a common cold or influenza?" Scandinavian investigators have found this question to be of very high sensitivity, but low specificity in studies of inhalation fever in wood trimmers and farmers (Malmberg et al., 1988). Specificity was improved by further inquiry related to the specific symptoms experienced, their duration and temporal relationship to work if the answer to this first question was answered affirmatively. Additional questions regarding respiratory symptoms (cough, phlegm production, wheezing), past respiratory illnesses, and cigarette smoking were included according to the standard format promulgated by the American Thoracic Society (ATS) (Ferris, 1978). At follow-up assessments, the workers were specifically asked about possible metal fume fever symptoms.

Physical examination consisted of the measurement of height, weight, oral temperature by digital thermometer (Becton Dickson, Franklin Lakes, NJ), respiratory rate, and auscultation of lung fields.

3.4.1.2 Chest Radiographs

Postero-anterior (PA) films only were taken on each worker pre and post-shift.

3.4.1.3 Spirometry

Spirometry was performed on all study subjects at each assessment. This consisted of a forced expiratory maneuver performed according to ATS (1995) standards. The one deviation from ATS criteria was that nose plugs were not worn by any of the study subjects.

All measurements were made using a portable spirometer (Welch Allyn PneumoCheck Model # 61000, Skanealeles Falls, NY) which provides automated statements regarding the quality of each maneuver. All subjects were

coached by the individual responsible for performing spirometry at the Baiyin Labour Institute who familiarized herself with ATS standards prior to the study. Most maneuvers were supervised by one of the investigators (CM).

Measurements included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV 1), forced expiratory flow (FEF 25-75%) and peak expiratory flow (PEF). The FEV 1/ FVC % was calculated from these measurements. Since the most useful measurements in establishing obstructive and restrictive changes are the FVC and FEV 1, these parameters only were used in subsequent analyses. Three acceptable maneuvers were required; the best FEV 1 and FVC may have been obtained from different maneuvers. A volume time loop was obtained for each of the best maneuvers. A representative spirometric tracing is shown in Figure 3.

At the conclusion of the study, the calibration of the spirometer was verified using a digital 3-liter Jones syringe (Table 2). All parameters were within 5% of the values obtained from the syringe, as stipulated by the ATS (1995).

3.4.2 Exposure Assessment

Exposure assessment consisted of external sampling through personal air sampling as well as measurement of zinc in serum and a cross-shift (approximately 8 hour) urine collection.

3.4.2.1 Personal Air Sampling

Personal air sampling was performed on all study subjects using Bendix Super Sampler BDX 44 pumps (Bendix Corporation, Baltimore, MD). Prior to the study, all samplers were calibrated using a rotameter that had undergone primary calibration with a bubble meter. Samplers operated at flow rates of between 1.3 to 2 liters per minute. The calibration of each sampler was verified just prior to each shift.

NAME: _____

DATE: 97.4.7 AM ID: 5

AGE: 30 HEIGHT: 171cm RACE: 1 SEX: M

	ACTUAL	NORM	%NORM	ABN
FVC	5.06	4.22	120	
FEV1	3.48	3.05	114	
FEV1/FVC%	74%	84%	94	
MEF25-75%	3.13	3.01	104	
BEST FVC	5.06	4.20	120	
BEST FEV1	4.06	3.53	115	

NORMS: Crapo 1981 (VS32P32)

Best FVC from 5 tries, 3 good.

Measurements corrected to BTPS.
Good FVC maneuver.

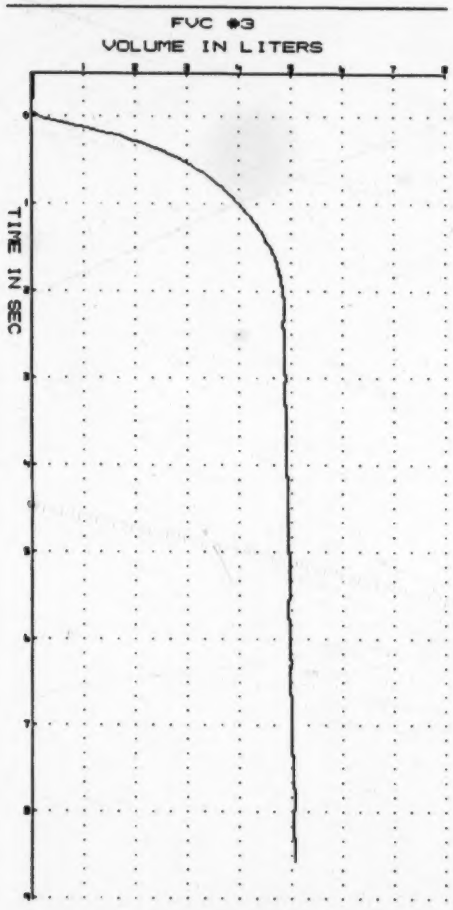

Figure 3: Representative Spirometric Tracing

Table 2: Calibration Data For Portable Spirometer

	Spirometer	Syringe	Percent Difference
FVC (L)	3.07	3	2
FEV_1 (L)	2.74	2.65	3
MMEF (L/Sec)	2.65	2.57	3
PEFR (L/Sec)	2.87	2.76	4
FEF 75 (L/Sec)		2.52	
FEF 50 (L/Sec)		2.68	
FEF 25 (L/Sec)		2.48	

Separate samples were taken during the first half of the shift in the morning and the second half in the afternoon. One sampler broke down during the study, therefore personal air sampling data are not available for subject #5 or subject #13 during the morning half of the shift. A replacement Chinese air sampler, designated sampler #5, was used for subjects #13 (afternoon half of the shift), #15, and #19.

Matched weight, mixed cellulose ester filters with a pore size of 0.8 μm in preloaded closed-faced 37 mm diameter cassettes (Omega Specialty Instrument Co., Chelm's Ford, MA) were used for all air sample collections. The system consists of two filters in each cassette that are certified to have the same weight within an acceptable margin. The sample is collected on the front filter, while the back filter can be used as a blank specimen. After sampling, the weight of the back filter can be subtracted from that of the front filter to determine the weight of the sample. Sample collection and analysis was performed according to the National Institute of Occupational Safety and Health (NIOSH, 1984) method 7030 for zinc. This method does not include a measurement of particle size and does

distinguish between zinc dust and fumes (NIOSH, 1984). No attempt to measure other exposures was made.

The cassette was attached to each pump and the flow rate calibration was verified before the sampler was placed on the worker. The pump was attached to each worker using a waist harness. The cassette was placed in the personal breathing zone, below the mid-clavicular area, just beyond the point where the chin would reach. Plastic tubing was used to connect the cassette to the pump and secured with duct tape. At the start of each shift the cap on the cassette was removed and the pump started.

When the shift was over, the pump was turned off and the cap replaced on the cassette. The cassette was secured shut with tape for transportation to the University of Alberta. For analysis, the two filters were separated and removed from each cassette in a manner to ensure that the integrity of the filter paper was preserved. Care was taken to ensure that only non-metal instruments were used to handle the filter papers directly. Filters were placed in an oven / dessicator for 20 to 25 minutes and allowed to acclimate to the laboratory's environment prior to being weighed on a microbalance. The weight of the back filter was subtracted from that of the front filter to determine the weight of the air sample.

The filters were then digested using nitric acid according to standard methods. All digests were diluted to a volume of 100 ml through the addition of distilled or de-ionized water. The digested samples were then given to the University of Alberta Hospitals Trace Elements / Environmental Toxicology Laboratory for analysis.

Field blanks were collected on each study day. These consisted of loaded filter cassettes that were attached to pumps on each day of the study. However, the pumps were not run and the filters were transported, digested, and analyzed at the University of Alberta in the same manner as the specimens from each worker. Two method blanks were also included in the analysis of air samples. These consisted of two samples that went through all the steps of digestion without the addition of filter specimens.

3.4.2.2 Urine Sampling

Cross shift urine samples were collected on each study subject. Workers were asked to void just prior to the shift and all urine produced until the end of the shift was collected. Specialized urine containers were not available, urine was collected in ceramic pots provided by the Baiyin Labour Institute. The volume of urine produced was measured by pouring the urine into a graduated cylinder. An approximately 25 ml sample was taken for analysis at the University of Alberta Hospitals Trace Elements / Environmental Toxicology Laboratory.

One field blank for urine was collected on each study day. This consisted of distilled water placed in the urine collection container and transferred to a smaller container for transportation and analysis at the University of Alberta in the same manner as the urine specimens. Urine samples were frozen prior to transportation.

3.4.2.3 Blood and Serum Sampling

Blood sampling was performed by venipuncture of the antecubital fossa using sterile techniques. Venous blood was collected into two evacuated containers for each subject. A 5 ml Vacutainer (Becton Dickson, Franklin Lakes, NJ) containing EDTA was used for the complete blood count.

A second Monoject container (Sherwood Medical, St. Louis, MO) without additives was used for serum sampling of trace elements. The Monoject container is required to avoid contamination of the sample, since zinc may be present in the rubber stopper of other evacuated containers. After being allowed to clot for approximately 1 hour, the Monoject container was spun at 3000 RPM for several minutes. The serum fraction was then transferred using plastic pipettes to plastic containers for transportation to the University of Alberta.

A small amount of blood (several drops) was taken from the Vacutainer for a hemoglobin determination and manual white cell count with differential

performed by a technician at the Baiyin Labour Institute. The remainder of the specimen was transported back to the University of Alberta.

Whole blood samples were kept refrigerated. Serum samples were refrigerated during transportation and were frozen after arrival at the University of Alberta.

No blanks were included for the serum samples. Blanks were used for the whole blood collection, since the rubber stopper of the Vacutainer tubes may have contaminated the specimens. These blanks were created by placing distilled water in the same type of Vacutainer and analyzing the water using the same methods as used for other elements in whole blood.

3.4.2.4 Measurement of Zinc and Other Elements

Measurement of zinc in serum, air sample digests, and urine was performed using flame atomic absorption spectrometry at the University of Alberta Hospital Trace Elements / Environmental Toxicology Laboratory. As preliminary data analysis suggested effects from co-exposures, an additional multi-element analysis was performed on serum, whole blood and urine samples using inductively coupled plasma – mass spectrometry (ICP-MS).

3.5 Data and Statistical Analyses

The concentration of zinc measured on the back filter was subtracted from that of the front filter to obtain the zinc concentration from each air sample. This value for the field blanks from each day of the study was then subtracted from the values obtained for each of the study subjects to obtain the final zinc concentration used for each subject. In those instances where subtraction of the back filter from the front filter resulted in a negative number for a field blank, the field blank value was taken as zero.

The concentration of zinc in each air sample digestion was measured in mg/L. Since the total volume of the digest was 0.1 L, the measured amount of

zinc (in milligrams) was obtained by dividing the measured concentration by 10. The volume of air was calculated by multiplying the calibrated flow rate (L/min) by the elapsed time (min) to obtain the volume (L). This volume was converted to m^3 through division by 1000 (Table 10).

Morning and afternoon air sampling results were analyzed separately and averaged to obtain mean values for the entire shift for each subject. For the purposes of obtaining an average value for subject 13, in whom only an afternoon air sampling result was available, a morning value of 0 mg/m^3 was used. This value was chosen in order to underestimate this individual's mean air exposure for the purposes of subsequent analyses of the relationship between zinc exposure and other parameters.

Urine zinc levels for statistical analyses were calculated by multiplying the measured concentration (in units of µmol/L) by the volume of urine collected to derive the amount of zinc in the cross-shift collection (in µmol) (Table 11). To compare to reference ranges, which are based on 24 hour collections, this value was multiplied by three.

Because of the small sample size, non-parametric methods were chosen to examine the relationship between zinc measured in air, serum, and urine using Spearman's rank correlation method. Two tailed tests of significance at the 0.05 level were used.

Blood indices were compared to air sample zinc measurements using analysis of variance (ANOVA). Additional analysis of the blood indices in relation to measurements of other elements was performed using a forward multiple linear regression.

No statistical adjustments were made for multiple comparisons. Data were analyzed using standard statistical packages (SAS Institute Inc., Cary, NC and SPSS Inc., Chicago, IL).

4. RESULTS

4.1 Clinical Assessment

4.1.1 Baseline Medical Interview and Examination

Information obtained from the baseline assessment of each worker is summarized in Table 3. All subjects were males with a mean age of 29.8 years. However, subject 4, the onsite safety supervisor, was ten years older than the next oldest participant.

All of the workers, with the exception of subjects 13 and 19, had worked in the foundry since its opening six years earlier in 1991. Many had worked in other foundries or other work sites operated by the Baiyin corporation prior to 1991. Subjects 2, 8 and 13 were the only participants never to have smoked. Subjects 8 and 11 were ex-smokers. The smoking history of subject 8 prior to quitting was not specified. Subject 11 had a seven pack year history (defined as the number of packs of cigarettes smoked on average each day multiplied by the number of years of smoking) prior to quitting in 1995. The remaining subjects were active smokers with an average history of 5.6 pack years.

Eleven subjects had a history of cough, answering "yes" to the question: Do you usually have a cough? Eleven had a history of phlegm production. Three of these eleven (subjects 9, 12, and 20) with phlegm production did not usually have a cough. Five had a history of wheezing. Two reported a past history of respiratory disease. The past condition was unspecified for subject 6, subject 15 reported an episode of childhood pneumonia.

Table 3: Data from Baseline Clinical Assessments

Subject #	Sex	Age (Yrs)	Length of Employment (Yrs)	Smoking History (Pack/Yr)	History of Cough (Yrs)	History of Phlegm (Yrs)	History of Wheezing	History of Other Respiratory Diseases
1	M	33	6	9	Yes (5)	Yes (5)	Yes	No
2	M	31	6	No	Yes (5)	No	No	No
3	M	31	6	Ex-smoker (NS*)	Yes (NS*)	No	No	No
4	M	44	6	5	Yes (NS*)	No	No	No
5	M	28	6		Yes (2)	Yes (NS*)	Yes	No
6	M	27	6	7	Yes (5)	Yes (5)	Yes	Yes (NS*)
7	M	34	6	10	Yes (4)	Yes (4)	No	No
8	M	28	6	No	No	No	No	No
9	M	27	6	4	No	Yes (2)	Yes	No
10	M	28	6	7	Yes (2)	Yes (3)	No	No
11	M	30	6	Ex-smoker (7)	Yes (5)	Yes (5)	Yes	No
12	M	26	6	7	No	Yes (3)	No	No
13	M	25	5.5	No	No	No	No	No
14	M	30	6	10	Yes (3)	Yes (3)	No	No
15	M	30	6	5	Yes (2)	Yes (2)		Yes (pneumonia)
16	M	24	6	4	No	No	No	No
17	M	29	6	5	No	No	No	No
18	M	30	6	2	No	No	No	No
19	M	33	1	4	No	No	No	No
20	M	27	6	5	No	Yes (2)	No	No
Mean		**29.8**	**5.7**					

NS* = not specified

Three subjects (numbers 8, 14, 18) gave a history of fever/chills in relation to work, two of these (subjects 8 and 14) also reported additional metal fume fever symptoms with these episodes of fever/chills (Table 4). These additional symptoms were not specifically elicited, the subjects were asked only if they had noted any other symptoms which they attributed to their work. In total, thirteen subjects reported at least one of the symptoms associated with metal fume fever (either nausea, dyspnea, cough, headache, sweet and/or metallic taste, throat irritation, or fatigue). When asked about symptoms noted when they first started work in the foundry, all but subject 11 (who recalled later experiencing work-related nausea) recalled symptoms. Ten experienced throat irritation, seven experienced sweet and/or metallic taste, four experienced cough, three experienced nausea, and three experienced dyspnea.

4.1.2 Follow-up Assessments

Data from the follow-up clinical assessments are shown in Tables 5 and 6. Also included is the number of hours off for each worker prior to the study shift. With the exception of subject 13, all workers had completed shifts within 48 hours of the study shift.

No increase in mean temperature was observed in the study subjects. The mean temperature at the pre-shift assessment was 36.2 °C, mid-shift: 36.7 °C, post-shift: 36.9 °C and 24 hours post-shift: 36.7 ° C. The highest individual measurement was 37.3°C.

Table 6 summarizes the remainder of the findings from the clinical assessments. Symptoms were specifically elicited as shown in the checklist on the final page of the questionnaire (Appendix 2). Five of the subjects did not report any symptoms in the course of the study. The only abnormality noted on physical examination was wheezes heard at the left lung base of subject 7 at the baseline examination. Nausea was a frequent complaint, reported by eight of

Table 4: History of Metal Fume Fever Symptoms

Subject Number	Fever/ Chills	Additional Symptoms	Symptoms Noted when First Started Work
1	-	-	sweet taste, throat irritation
2	-	-	cough, dyspnea
3	-	-	throat irritation
4	-	-	nausea, throat irritation
5	-	nausea, dyspnea	nausea, throat irritation
6	-	-	dyspnea
7	-	cough	cough, throat irritation
8	+	headache, sweet taste	throat irritation
9	-	sweet, metallic taste	sweet metallic taste
10	-	cough	sweet taste, cough
11	-	nausea	-
12	-	sweet, metallic taste	sweet taste, nausea
13	-	sweet, metallic taste	sweet, metallic taste
14	+	nausea, dizziness, cough	throat irritation
15	-	nausea	cough
16	-	throat irritation	throat irritation
17	-	-	dyspnea
18	+	-	throat irritation, sweet taste
19	-	fatigue	throat irritation, sweet taste
20	-	fatigue	throat irritation, sweet taste

Table 5: Temperature Measurements from Clinical Assessments

Subject	Hours Since Last shift	Oral Temperature (°C)			
		Pre-shift	Mid-shift	Post-shift	24 hours post-shift
1	16	34.8	36.4	37.0	36.6
2	16	35.5	36.7	37.0	36.5
3	16	36.2	36.4	37.2	36.6
4	16	36.4	37.1	37.0	37.0
5	16	36.0	36.7	36.7	36.8
6	16	36.1	36.8	37.0	36.5
7	36	36.7	36.8	36.9	37.0
8	16	36.6	36.7	36.4	35.9
9	16	36.2	36.0	36.5	36.7
10	24	36.4	36.9	37.0	36.7
11	24	36.5	36.9	37.2	36.8
12	24	35.2	37.1	36.8	36.0
13	56	36.4	36.3	36.8	36.8
14	36	36.9	37.0	37.2	37.1
15	24	36.8	36.7	36.9	36.9
16	24	35.7	36.9	36.9	36.9
17	24	36.5	37.0	37.3	36.6
18	24	36.3	36.9	36.8	36.9
19	24	36.3	36.6	37.1	36.1
20	12	35.9	36.7	36.8	36.7
Mean		**36.2**	36.7	36.9	36.7

Table 6: Data from Clinical Assessments

Subject	Hours Since Last Shift	Signs and Symptoms Reported
1,2,3	16	None.
4	16	Post-shift: Nausea.
5	16	Mid-shift, post-shift, 24 hrs post-shift: nausea.
6	16	Mid-shift: chest tightness, nausea. Post-shift: dry cough, chest tightness, throat irritation. 24 hrs post-shift: dry cough, chest tightness.
7	36	Baseline: expiratory wheeze left lung base. Mid-shift: productive cough. Post-shift: productive cough. 24 hrs post-shift: productive cough, nausea.
8	16	Mid-shift: productive cough, sweet/metallic taste, headache. Post-shift: chest tightness. 24 hrs post shift: chest tightness.
9	16	Mid-shift , post-shift: chest tightness, sweet/metallic taste.
10	24	None.
11	24	Mid-shift, post-shift: nausea, sweet/metallic taste. 24 hrs post-shift: throat irritation, chest tightness.
12	24	Post-shift: sweet/metallic taste.
13	56	Mid-shift, post-shift: sweet/metallic taste.
14	36	Mid-shift: myalgias, nausea, headache, feverish. Post-shift: productive cough. 24 hrs post-shift: nausea.
15	24	Mid-shift, post-shift, 24 hrs post-shift: throat irritation, chest tightness, nausea.
16	24	Post-shift: productive cough, chest tightness.
17	24	Mid-shift: dyspnea, cough. Post-shift: cough, throat irritation.
18	24	None.
19	24	Mid-shift: throat irritation, sweet/metallic taste.
20	12	Mid-shift: throat irritation, productive cough, chest tightness, nausea.

the subjects. A sweet or metallic taste was reported by six workers during the study. Six workers developed throat irritation. In total, ten workers reported respiratory symptoms (cough, chest tightness, or dyspnea).

4.1.3 Chest Radiographs

Chest radiographs before and after the shift were interpreted by a physician. No relevant abnormalities or changes between the two films were noted.

4.1.4 Spirometry

Individual spirometric values are presented in Tables 7 through 10. Predicted values of Crapo et al. (1981) were used for subjects 1 through 9, while those of Knudsen et al. (1983) were used in subjects 10 to 20. The change in predicted values occurred as a result of an unintentional switch in the spirometer's settings. Racial adjustment was used for all predicted values. There was no evidence of restrictive patterns in any of measurements. All subjects had FVC's above 100% predicted with the exception of subject 4 whose FVC was between 87% and 95% predicted. Individual abnormalities were noted for subjects 4 and 6 which were consistent and observed at the assessments before, during and 24 hours after the work shift. According to the ATS (1991) interpretation guidelines, subjects 4 and 6 showed evidence of mild obstruction. Subject 4 had an FEV1/FVC% of 71 to 75% and an FEV1 of 79 to 84% predicted. Subject 6 had an FEV1/FVC% of between 56 and 59% and an FEV1 of 80 to 92% predicted.

Mean best FEV1 and FVC increased throughout the protocol, as summarized in Table 11. Mean FEV1 increased by 0%, 2%, and 3% of the pre-shift measurement at the mid-shift, post-shift, and 24 hour post-shift assessments. Similarly, mean FVC increased by 2%, 5%, and 6%.

Table 7: Individual Results From Pre-Shift Spirometry

Subject	FVC	FEV1	FEV1/FVC%	FEF 25-75%	PEF	Best FVC	Best FEV1
1	4.46	3.16	71%	2.51	4.54	4.46	3.16
2	4.32	3.17	74%	2.08	9.69	4.32	3.17
3	5.19	4.11	79%	3.68	8.73	5.23	4.11
4	3.52	2.5	71%	1.57	7.94	3.52	2.5
5	5.06	3.99	79%	3.53	7.69	5.06	4.08
6	5.03	2.82	56%	1.46	6.11	5.03	2.87
7	4.47	3.68	82%	3.89	7.51	4.47	3.68
8	4.77	4.11	86%	4.55	9.18	4.77	4.11
9	3.98	2.64	66%	1.31	5.93	3.98	2.7
10	4.24	3.55	84%	3.62	11.43	4.24	3.55
11	4.37	3.84	88%	4.66	7.64	4.57	3.84
12	4.25	3.84	90%	3.88	8.29	4.28	3.84
13	4.53	3.88	86%	4.49	8.87	4.53	3.88
14	4.51	3.79	84%	4.14	5.74	4.51	3.87
15	5.38	4.23	79%	3.69	8.72	5.38	4.23
16	4.63	4.22	91%	4.86	11.48	4.7	4.22
17	5.4	4.08	76%	3.36	8.34	5.4	4.08
18	4.6	3.69	80%	3.96	9.24	4.6	3.69
19	5.28	4.6	87%	5.45	8.05	5.28	4.6
20	5.33	3.79	71%	2.41	7.76	5.33	3.83
Mean	4.67	3.68	79%	3.46	8.14	4.68	3.70

Table 8: Individual Results from Mid-Shift Spirometry

Subject	FVC	FEV1	FEV1/FVC%	FEF 25-75%	PEF	Best FVC	Best FEV1
1	4.37	3.74	85%	4.35	8.52	4.37	3.74
2	4.04	3.22	80%	3.19	10.78	4.04	3.22
3	5.58	4.45	80%	4.12	9.46	5.58	4.45
4	3.69	2.67	72%	1.78	8.99	3.72	2.67
5	4.94	4.03	82%	3.81	8.06	4.97	4.03
6	4.97	2.92	59%	1.66	5.56	4.97	2.92
7	4.42	3.71	84%	4.23	8.41	4.42	3.71
8	5.09	4.34	85%	4.79	8.52	5.09	4.34
9	4.03	3.35	83%	3.54	6.61	4.03	3.35
10	4.12	3.56	86%	3.75	10.54	4.14	3.56
11	4.8	4.16	87%	4.88	9.61	4.8	4.16
12	4.32	3.85	89%	3.86	8.38	4.32	3.91
13	4.5	3.84	85%	4.22	8.9	4.5	3.84
14	4.46	3.89	87%	4.76	6.44	4.69	3.89
15	5.47	4.35	80%	3.86	8.95	5.47	4.35
16	4.17	3.86	93%	4.3	7.38	4.17	3.86
17	5.13	3.27	64%	2.2	8.4	5.28	3.27
18	4.7	3.76	80%	3.69	8.79	4.7	3.76
19	5.49	4.83	88%	5.8	11.54	5.49	4.83
20	4.71	3.59	76%	2.99	8.42	4.71	3.59
Mean	4.65	3.77	81%	3.79	8.61	4.67	3.77

Table 9: Individual Results from Post-Shift Spirometry

Subject	FVC	FEV1	FEV1/FVC%	FEF 25-75%	PEF	Best FVC	Best FEV1
1	4.35	3.69	85%	4.22	9.31	4.35	3.69
2	4.3	3.21	75%	2.34	11.29	4.3	3.21
3	5.81	4.41	76%	3.59	9.61	5.81	4.41
4	3.61	2.58	72%	1.66	8.01	3.61	2.6
5	5	4.14	83%	3.91	8.87	5	4.14
6	4.99	2.89	58%	1.6	5.73	5.18	2.89
7	4.86	4.07	84%	4.6	8.42	4.86	4.07
8	4.91	4.11	84%	4.22	9.51	4.91	4.11
9	4.16	3.26	78%	2.88	6.78	4.16	3.26
10	4.09	3.48	85%	3.68	12.08	4.1	3.48
11	5.03	4.28	85%	5.17	9.12	5.03	4.28
12	4.26	3.92	92%	4.46	7.9	4.26	3.92
13	4.6	3.88	84%	4.29	8.88	4.6	3.88
14	4.62	4.09	89%	5.33	8.81	4.62	4.09
15	5.52	4.52	82%	4.34	8.76	5.62	4.52
16	4.78	4.34	91%	6.45	11.19	4.79	4.34
17	5.4	3.96	73%	3.07	7.68	5.44	3.96
18	4.42	3.73	84%	4.17	8.97	4.44	3.73
19	5.69	5.08	89%	6.45	12.42	5.69	5.08
20	4.9	4.05	83%	4.29	9.64	4.9	4.05
Mean	4.77	3.88	82%	4.04	9.15	4.78	3.89

Table 10: Individual Results from Spirometry 24 Hours Post-Shift

Subject	FVC	FEV1	FEV1/FVC%	FEF 25-75%	PEF	Best FVC	Best FEV1
1	4.3	3.69	86%	3.93	9.99	4.31	3.69
2	4.4	3.24	74%	2.15	11.28	4.4	3.24
3	5.36	4.11	77%	3.41	9.3	5.36	4.11
4	3.36	2.51	75%	1.87	7.97	3.36	2.51
5	5.06	3.87	76%	3.16	8.87	5.06	3.87
6	5.54	3.27	59%	1.85	6.59	5.54	3.27
7	4.86	3.97	82%	4.08	6.93	4.91	3.97
8	4.98	4.16	84%	4.2	9.39	4.98	4.17
9	4.1	3.36	82%	3.27	7.37	4.1	3.37
10	4.39	3.74	85%	4.07	12.9	4.39	3.76
11	5.16	4.47	87%	5.36	8.77	5.16	4.47
12	4.6	4.19	91%	4.32	8.81	4.6	4.19
13	4.82	4.09	85%	4.88	9.15	4.82	4.09
14	4.76	4.2	88%	5.56	8.39	4.76	4.2
15	5.8	4.55	78%	4.07	8.86	5.8	4.55
16	4.85	4.55	94%	6.65	11.64	4.85	4.55
17	5.21	4.07	78%	3.93	10.06	5.36	4.1
18	4.12	3.58	87%	4.56	8.3	4.23	3.58
19	5.41	4.71	87%	5.62	10.06	5.41	4.71
20	4.6	3.81	83%	3.73	10.1	4.6	3.81
Mean	4.78	3.91	82%	4.03	9.24	4.80	3.91

Table 11: Mean Values from Spirometry at Each Assessment

(Percentage increase in FVC and FEV1 from pre-shift measurement shown in brackets)

	Pre-Shift	Mid-Shift	Post-Shift	24 Hours Post Shift
FVC	4.67	4.65	4.77	4.78
FEV1	3.68	3.77	3.88	3.91
FEV1/FVC%	79	81	82	82
FEF 25-75%	3.46	3.79	4.04	4.03
PEF	8.14	8.61	9.15	9.24
Best FVC	4.68	4.67 (0)	4.78 (+2%)	4.80 (+3%)
Best FEV1	3.7	3.77 (+2%)	3.89 (+5%)	3.91 (+6%)

4.2 Exposure Assessment

The amount of zinc measured by atomic absorption spectrometry is plotted against the mass of each particulate sample obtained by weighing the filter in Figure 4. Under a linear regression model, there was a strongly significant association between these two parameters ($p < 0.001$, $r = 0.60$).

4.2.1 Personal Air Sampling

Air sampling levels of zinc were generally low (Tables 12, 13, 14). However, for three subjects, the mean exposure exceeded the recommended 8 hour TLV. These were subject 8 (11.2 mg/m^3), subject 14 (18.6 mg/m^3), and subject 15 (7.3 mg/m^3). Elevated half-shift exposures were identified for subject 8 (AM shift: 5.2 mg/m^3, PM shift: 17.2 mg/m^3), subject 13 (PM shift: 5.9 mg/m^3), subject 14 (PM shift: 36.3 mg/m^3), subject 15 (AM shift: 9.8 mg/m^3, PM shift: 4.8 mg/m^3), and subject 19 (PM shift: 6.7 mg/m^3). The mean of the 18 available morning shift air sampling results was 1.8 mg/m^3 compared to a mean of 4.5 mg/m^3 for the 19 available afternoon air shift samples.

4.2.2 Urine Samples

Calculated 24 hour urine zinc levels ranged from 2.6 to 24.9 µmol (Table 14). Subjects 3 (24.9 µmol) and 19 (22.4 µmol) had values above the reference range. A widely accepted reference range for zinc in urine is 2.3 to 18.4 µmol for a 24 hour collection (Milne, 1994).

For statistical analysis, the total amount of zinc excreted during the shift was used. There was a statistically significant association ($p = 0.04$) between mean air sampling values of zinc and urine zinc measured during the shift with a rank correlation coefficient (rho) of 0.47. When analyzed separately, this association was driven more by the afternoon shift air

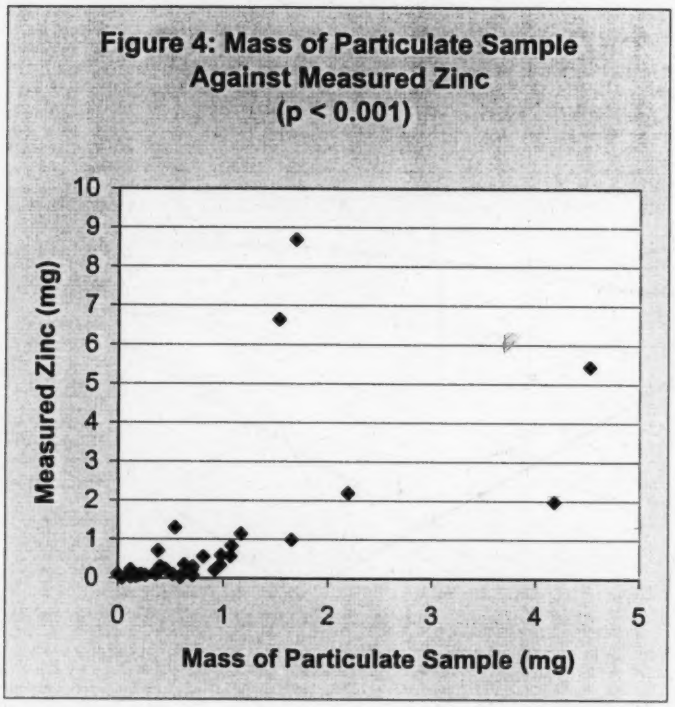
Figure 4: Mass of Particulate Sample Against Measured Zinc (p < 0.001)
Measured Zinc (mg)
10
9
8
7
6
5
4
3
2
1
0
0
1
2
3
4
5
Mass of Particulate Sample (mg)

Table 12: Calculation of Amount of Zinc in Air Samples

Sample No	Zinc Concentration (mg/L)				
	Front Filter	Back Filter	Difference	Difference from Field Blank	Net Measurement
1	0.21	0.078	0.132	0.214	0
2	2.195	0.038	2.157	0.012	2.145
3	0.502	0.066	0.436	0.214	0.222
4	1.445	0.054	1.391	0.012	1.379
5	0.965	0.033	0.932	0.214	0.718
6	2.56	0.018	2.542	0.214	2.328
7	1.25	0.034	1.216	0.214	1.002
8	1.215	0.053	1.162	0.214	0.948
9	2.32	0.03	2.29	0.214	2.076
10(1)	0.054	0.042	0.012	-	-
11	3.395	0.023	3.372	0.012	3.36
12	0.929	0.087	0.842	0.012	0.83
13	11.6	0.043	11.56	0.214	11.346
14	0.519	0.048	0.471	-0.016	0.471
15	9.95	0.008	9.942	-0.016	9.942
16	0.658	0.008	0.65	-0.016	0.65
17(2)	0.023	0.039	-0.016	-	
18	0.904	0.036	0.868	-0.016	0.868
19	0.767	0.037	0.73	0.012	0.718
20	2.48	0.05	2.43	0.012	2.418
21	22.1	0.068	22.032	-0.016	22.032
22	2.33	0.019	2.311	0.012	2.299
23(3)	0.021	0.019	0.002	-	-
24(4)	0.024	0.026	-0.002	-	-
25	0.383	0.054	0.329	-0.016	0.329

1. Field blank from first day of study.
2. Field blank from secon day of study.
3. Additional field blank, not used in data analysis.
4. Field blank from third day of study.

Table 12: Calculation of Amount of Zinc in Air Samples

Sample No	Zinc Concentration (mg/L)				
	Front Filter	Back Filter	Difference	Difference from Field Blank	Net Measurement
26	3.055	0.057	2.998	0.012	2.986
27	8.8	0.542	8.258	-0.001	8.258
28	0.962	0.037	0.925	-0.002	0.925
29	2.2	0.027	2.173	-0.001	2.173
30	5.51	0.033	5.477	-0.002	5.477
31	3.01	0	2.972	-0.001	2.972
32	0.865	0.035	0.83	-0.001	0.83
33(5)	0.028	0.029	-0.001	-	-
34	54.5	0.124	54.376	-0.001	54.376
35	5.7	0.036	5.664	-0.002	5.664
36(6)	0.252	0.038	0.214	-	-
37	20	0.21	19.79	-0.001	19.79
38	3.518	0.056	3.462	-0.001	3.462
39	5.93	0.057	5.873	-0.002	5.873
40	8.73	0.043	8.687	-0.002	8.687
41	6.68	0.041	6.639	-0.002	6.639
42	1.38	0.078	1.302	-0.001	1.302
43	0.747	0.047	0.7	-0.002	0.7
44(7)	0.045	0.067	-0.022	-	-
45(7)	0.062	0.037	0.025	-	-

5. Field blank from fourth day of study.
6. Field blank from fifth day of study.
7. Method blank.

Table 13: Calculation of Zinc Concentration in Air Samples

(Blanks not included)

Air Sample No.	Zinc Concentration (mg/L)	Zinc (mg)	Flow Rate (L/min)	Elapsed Time (min)	Volume (L)	Volume (m3)	Zinc Concentration (mg/m3)
1	0	0	1.5	105	157.5	0.158	0
2	2.14	0.214	1.8	150	270	0.270	0.79
3	0.22	0.022	1.5	165	247.5	0.248	0.90
4	1.38	0.138	1.3	144	187.2	0.187	0.74
5	0.72	0.072	1.3	165	214.5	0.215	0.33
6	2.33	0.233	1.3	168	218.4	0.218	1.1
7	1.00	0.100	1.5	140	210	0.210	0.48
8	0.95	0.095	1.5	146	219	0.219	0.43
9	2.08	0.208	1.3	165	214.5	0.215	0.97
10							
11	3.36	0.336	1.3	140	182	0.182	1.8
12	0.83	0.083	1.3	120	156	0.156	0.53
13	11.35	1.135	1.5	113	169.5	0.170	6.7
14	0.47	0.047	1.3	152	197.6	0.198	0.24
15	9.94	0.994	1.5	128	192	0.192	5.2
16	0.65	0.065	1.5	143	214.5	0.215	0.30
17							
18	0.87	0.087	1.3	119	154.7	0.155	0.56
19	0.72	0.072	1.3	89	115.7	0.116	0.62
20	2.42	0.242	1.6	139	222.4	0.222	1.09

Table 13: Calculation of Zinc Concentration in Air Samples.
(Blanks not included)

Air Sample No.	Zinc Concentration (mg/L)	Zinc (mg)	Flow Rate (L/min)	Elapsed Time (min)	Volume (L)	Volume (m3)	Zinc Concentration (mg/m3)
21	22.03	2.203	1.5	85	127.5	0.128	17
22	2.30	0.230	1.5	142	213	0.213	1.1
23							
24							
25	0.33	0.033	1.5	98	147	0.147	0.22
26	2.99	0.299	1.5	125	187.5	0.188	1.6
27	8.26	0.826	1.5	116	174	0.174	4.8
28	0.93	0.093	1.5	125	187.5	0.188	0.49
29	2.17	0.217	1.5	165	247.5	0.248	0.88
30	5.48	0.548	1.6	113	180.8	0.181	3.0
31	2.97	0.297	1.3	113	146.9	0.147	2.0
32	0.83	0.083	1.5	117	175.5	0.176	0.47
33							
34	54.38	5.438	1.5	100	150	0.150	36
35	5.66	0.566	1.3	141	176.2	0.176	3.2
36							
37	19.79	1.979	1.5	135	202.5	0.203	9.8
38	3.46	0.346	1.5	117	175.5	0.176	2.0
39	5.87	0.587	1.6	140	224	0.224	2.6
40	8.69	0.869	1.5	98	147	0.147	5.9
41	6.64	0.664	1.5	125	187.5	0.188	3.5
42	1.30	0.130	1.3	113	146.9	0.147	0.89
43	0.70	0.070	1.3	78	97.5	0.098	0.72

Table 14: Zinc Measurements in Air, Serum, and Urine

Subject No	AM Air Sample Zinc Concentration (mg/m3)	PM Air Sample Zinc Concentration (mg/m3)	Mean Air Sample Zinc Concentration (mg/m3)	Serum Zinc (umol/L)	Urine Zinc (umol/L)	Urine Vol. (ml) approx. 8 hr	Urine Zinc (umol/V) approx. 8 hr	Urine Zinc (umol/V) 24 hr
1	0.62	0.53	0.58	10.3	29.1	65	1.89	5.67
2	0.74	1.9	1.3	12.2	20.8	265	5.51	16.5
3	0.79	1.1	0.94	12.1	10.9	760	8.28	24.8
4	1.6	1.1	2.7	11.5	17.7	240	4.25	12.7
5	not available	not available		15.8	10.5	280	2.94	8.82
6	0.89	2.0	1.5	11.5	11.6	360	4.18	12.5
7	0.24	0.56	0.40	12.5	2.4	770	1.85	5.54
8	5.2	17	11	12	27	170	4.59	13.8
9	0.30	0.22	0.26	10	13.4	65	0.87	2.61
10	2.6	3.0	2.8	9.1	15.2	330	5.02	15.1

Table 14: Zinc Measurements in Air, Serum, and Urine

Subject No	AM Air Sample Zinc Concentration (mg/m3)	PM Air Sample Zinc Concentration (mg/m3)	Mean Air Sample Zinc Concentration (mg/m3)	Serum Zinc (umol/L)	Urine Zinc (umol/L)	Urine Vol. (ml) approx. 8 hr	Urine Zinc (umol/V) approx. 8 hr	Urine Zinc (umol/V) 24 hr
11	3.5	0.49	2.0	12.4	17.5	190	3.33	9.98
12	3.2	0.72	2.0	9.9	12.9	210	2.71	8.13
13	not available	5.9	3.0	13.6	42.9	65	2.79	8.37
14	0.88	36.2	18	12.3	12	190	2.28	6.84
15	9.8	4.8	7.3	10.6	11.7	320	3.74	11.2
16	0.47	2.0	1.2	11	5.9	620	3.66	11.0
17	0.33	0.09	0.21	12.1	16	130	2.08	6.24
18	0.97	1.1	1.0	11.8	10.7	310	3.32	9.95
19	0.43	6.7	3.6	9.3	11	680	7.48	22.4
20	0.48	0	0.24	10.2	16.5	160	2.64	7.92

sample (rho = 0.55, p= 0.015) rather than the morning sample (rho = 0.41, p = 0.091). Figure 5 is a plot of the mean air sample zinc measurement against the measured value of zinc in the cross-shift urine collection for each subject.

4.2.3 Serum Samples

Serum zinc levels ranged from 9.1 to 15.8 μmol/L (Table 12). These values fall within or below the plasma reference range of 10.7 to 22.9 μmol/L, recognizing that serum levels of zinc may be as much as 16% higher than plasma levels.

No statistically significant association was observed between serum zinc levels and air sample levels at any time (p = 0.84, r = 0.05, Figure 6).

4.2.4 Blood Indices

Blood indices for each subject are summarized in Table 15. All hemoglobin concentrations were within accepted normal values for men, with the exception of subject 8 (104 g/L). All white cell counts were within normal limits. The highest measured value was that of subject 17 (10.8×10^9 cells/L). With respect to the differential white cell count, the percentage of neutrophils (polymorphonuclear leukocytes) was generally at or above the upper limit of normal (60%). The remaining differentials were within normal limits.

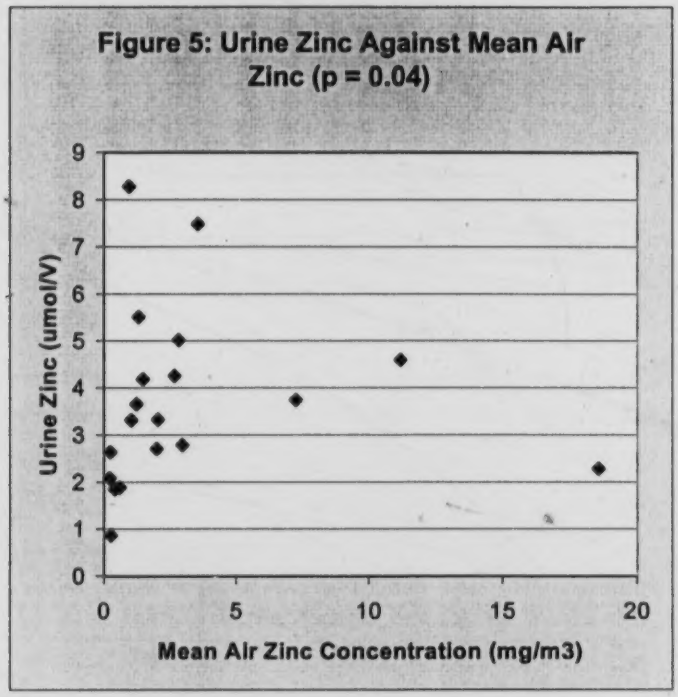
Figure 5: Urine Zinc Against Mean Air Zinc (p = 0.04)
Urine Zinc (umol/V)
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
Mean Air Zinc Concentration (mg/m3)

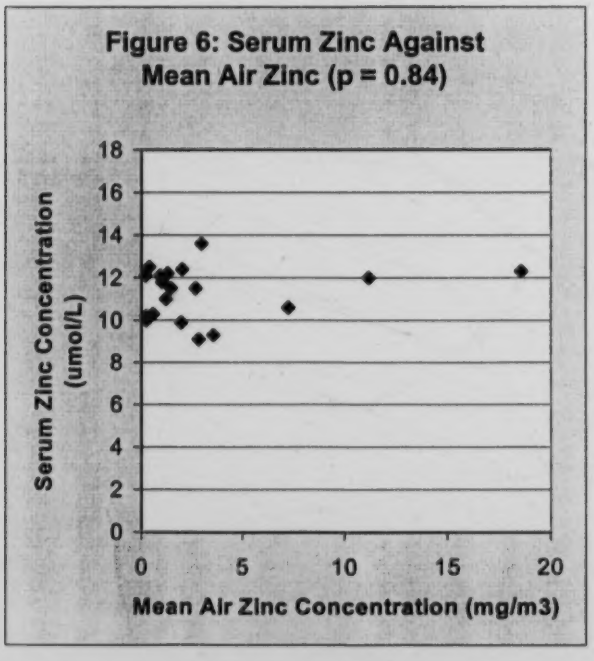
Figure 6: Serum Zinc Against Mean Air Zinc (p = 0.84)
Serum Zinc Concentration (umol/L)
0
2
4
6
8
10
12
14
16
18
0
5
10
15
20
Mean Air Zinc Concentration (mg/m3)

Table 15: Individual Blood Indices

Date of Study	Subject Number	WBC (x 10^9/L)	Hgb (g/L)	% N[(1)]	% L[(2)]	% M[(3)]	% E[(4)]	% B[(5)]
14-Jun	1	9.3	162	0.63	0.35	0.02		
	2	8.1	178	0.60	0.38	0.01	0.01	
	3	7.8	145	0.61	0.37	0.01		0.01
	4	5.9	171	0.67	0.31	0.01	0.01	
15-Jun	5	6.8	169	0.57	0.41	0.02		
	7	8.4	175	0.68	0.29	0.01	0.02	
	8	8.2	104	0.68	0.32			
	9	6.7	168	0.57	0.42		0.01	
16-Jun	10	8.1	151	0.63	0.37			
	11	7.8	149	0.68	0.31	0.01		
	12	5.8	162	0.56	0.42	0.01	0.01	
	13	8.9	166	0.61	0.38	0.01		
17-Jun	6	8	154	0.58	0.41	0.01		
	14	5	140	0.73	0.26		0.01	
	15	8.8	160	0.68	0.32			
	16	7.3	155	0.59	0.39	0.02		
18-Jun	17	10.8	175	0.58	0.42			
	18	9.6	168	0.68	0.3		0.01	0.01
	19	7.4	170	0.59	0.4	0.01		
	20	9.8	152	0.6	0.38	0.01		0.01

(1) Percentage neutrophils
(2) Percentage lymphocytes
(3) Percentage monocytes
(4) Percentage eosinophils
(5) Percentage basophils

5. DISCUSSION

Although several statistically significant associations were found in this study, examination of the plots shows that these associations are driven by the three subjects with the highest mean air zinc exposures. The remaining 16 subjects had air exposures less than 5 mg/m^3 . Thus, all of the associations discussed below must be interpreted with caution in view of the small sample size.

5.1 Distinguishing Metal Fume Fever From Toxic Pneumonitis[2]

In addition to metal fume fever, a more serious toxic or chemical pneumonitis can result from the inhalation of the oxides of several metals. The prototype for this pattern of diffuse, profound alveolar damage is cadmium (Blejer et al., 1966; Barnhart and Rosenstock, 1984) although the oxides of mercury (Rowens et al., 1991) and beryllium (Kriebel et al., 1988) are also established causes.

Manganese oxide is often included as a cause of acute pneumonitis (See Nemery, 1990). The term "manganese pneumonitis" was coined by Lloyd Davis (1949) referring to increased rates of pneumonia in exposed workers. His rationale for the use of this term was twofold. Animal studies that he had performed on mice had shown an intense inflammatory response following the inhalation of maganese dioxide dust (Lloyd Davis, 1949). The dose administered to the animals was reported to contain up to 2786 dust particles per cm^3 for 2 hours a day and also contained 9.6% KOH (Lloyd Davis, 1946). It is not possible to directly compare this measurement to concentrations based on mass determinations. However, given technical constraints present at that time in the determination of particle size, the concentration may have been quite high. His second argument was based on the observation that exposed workers also

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2 A version of this chapter has been published. Martin CJ, Guidotti TL, Langård S, (1997). Respiratory hazards of welding. Clin Pulm Med 4(4):194-204.

experienced nasopharyngitis and bronchitis, suggesting an irritant effect on the upper respiratory tract. Even allowing for this argument, the inclusion of manganese as a cause of acute pneumonitis seems to have been the result of semantic confusion and is not warranted since manganese has not been reported to cause acute parenchymal lung damage.

The clinical picture of acute toxic pneumonitis from metal oxides consists of an insidious course of non-cardiogenic pulmonary edema and adult respiratory distress syndrome (ARDS). This condition may be life threatening and supportive treatment is often required. However, the onset of ARDS can be delayed by up to 48 hours from the time of exposure. During this prodromal period, the signs and symptoms of toxic metal pneumonitis are very similar to those of metal fume fever. For this reason, some advocate inclusion of cadmium pneumonitis in the differential diagnosis of any individual presenting with the clinical picture of metal fume fever (Barnhart and Rosenstock, 1984).

Furthermore, there is convincing evidence that low level exposure to cadmium oxide can cause a self-limited illness indistinguishable from metal fume fever (Johnson and Kilburn, 1983). This may be the reason why metals such as cadmium and mercury are frequently included as causes of metal fume fever.

The available observations suggest that a continuum of clinical presentations exists between metal fume fever and toxic metal pneumonitis, with considerable overlap between the two. Key factors determining the extent of pulmonary involvement include the inherent toxicity of the metal involved and the level of exposure. Low level inhalational exposure to more toxic metals such as mercury and cadmium can cause a self-limited, flu-like illness indistinguishable from metal fume fever. Conversely, high level exposure to a less toxic metal such as zinc can result in significant functional and radiographic changes, as in the case report by Langham Brown (1987). The case reports and investigations are summarized in Table 16, which compares and contrasts metal fume fever and toxic pneumonitis (Adapted from Blanc, personal communication, 1996).

Table 16: Comparison of features of metal fume fever and toxic metal pneumonitis. (Adapted from Blanc, personal communication).

	Metal Fume Fever **Prototype: Zine Oxide**	**Toxic Metal Pneumonitis** **Prototype: Cadmium**
	Dose Related	Dose related
Onset:	4-8 hours post exposure	4-8 hours post exposure
Fever:	*Sine Qua Non*	Common
Chest Radiograph:	Normal or Fleeting infiltrates	Non-cardiogenic pulmonary edema
Arterial Blood Gases:	Normal or minimal transient changes	Marked hypoxia, widened Alveolar-arterial gradient
Complete Blood Count:	Polymorphonuclear leukocytosis	Polymorphonuclear leukocytosis
Pulmonary Function Testing:	Normal or transient changes	Frank restrictive defect
Bronchoalveolar Lavage:	Polymorphonuclear leukocytosis	Polymorphonuclear leukocytosis
Prognosis:	Self-limiting	Life threatening
Sequelae:	? None	Post-Adult Respiratory Distress Syndrome

The above discussion has been restricted to exposure to metals in the form of oxides. However, acute pneumonitis can also be the result of inhalation of several metallic compounds. In a recent case report by Blount (1990) entitled "Two types of metal fume fever: mild vs serious", the etiologic agent was zinc chloride, used in military smoke bombs. The affected individual developed acute respiratory distress and non-cardiogenic pulmonary edema, a clinical picture more compatible with toxic pneumonitis. In this case the pulmonary damage is more likely attributable to the halide ion rather than zinc (Nemery, 1990). Nevertheless, zinc chloride is frequently equated with zinc oxide and included as a cause of metal fume fever (See Walsh et al., 1994).

In summary, the term metal fume fever is used quite loosely resulting in considerable confusion. Since inhalation of the oxides of cadmium and mercury can be fatal, associating these metals with metal fume fever can result in a false sense of security on the part of both worker and physician. In one case report, acute cadmium pneumonitis was misdiagnosed as metal fume fever by the attending physicians even though a history of exposure to cadmium was available (Ando et al., 1995). The term metal fume fever should be reserved for suspected exposures to zinc, copper and magnesium although one recent study casts serious doubt on the ability of magnesium to produce this disease (Kuschner et al., 1997). Alternatively, the word "metal" could be substituted by the specific agent of concern, such as zinc fume fever and cadmium fume fever, recognising that the two illnesses can have very divergent prognoses.

5.2 Clinical Assessment of Workers

Although symptoms suggestive of metal fume fever were recalled by two (fever/chills with additional symptomatology) or possibly three (fever/chills alone) workers, no cases were observed in the course of the study. Subject 14 reported a constellation of symptoms (myalgias, nausea, headache, feeling feverish)

consistent with metal fume fever at the mid-shift assessment. However, these symptoms were not noted at subsequent assessments and were not accompanied by either a rise in oral temperature or the number of peripheral leukocytes.

Metal fume fever has been reproduced in eleven of twelve naïve subjects breathing zinc oxide at a concentration of 5 mg/m^3 over two hours (Fine et al., 1997). Three subjects in the present study had cumulative eight hour exposures of 7.5 (subject 15), 11.2 (subject 8) and 18.6 (subject 14) mg/m^3. Thus, despite sufficient exposure, metal fume fever did not develop in the workers studied. Two mechanisms can be invoked to explain this finding.

The first relates to the well known rapidly acquired tolerance to zinc exposure, termed tachyphylaxis. The precise duration of tachyphylaxis in the absence of ongoing exposure is not known. It has been demonstrated in human subjects receiving a second zinc exposure given within 24 hours of the first exposure (Drinker et al. II, 1927). Anecdotally, workers recognize that it is lost after weekends. Subject 8 had finished a shift 16 hours previously, subject 14 had finished a shift 36 hours previously, and subject 15 had finished a shift 24 hours previously. Therefore, it is quite possible that tachyphylaxis may explain why no cases of metal fume fever were observed.

A second less well recognized tolerance may also be operative over a longer time course. Investigators of organic dust toxic syndrome both in swine confinement workers and grain dust handlers have noted that new employees seem to be more susceptible to the development of inhalation fever (Malmberg et al., 1993; doPico et al., 1984). Recent unpublished work has provided experimental support for a similar phenomenon in zinc exposure. In this study, workers from a galvanized sheet metal shop were found to have fewer symptoms, less of a rise in temperature and less of an increase in levels of serum IL-6 following exposure to 5 mg/m^3 over 2 hours compared to naïve subjects receiving the same exposure(Terry Gordon, personal communication, November, 1997). Very little is known regarding this longer term tolerance.

However, if these findings are confirmed, such tolerance would be expected to be present in this study population.

Another possible explanation for the absence of metal fume fever in the study subjects relates to selection bias. All of the workers studied had worked in the foundry for many years. It is possible that workers particularly susceptible to the development of metal fume fever left the workplace, with those workers remaining being relatively tolerant to the development of metal fume fever.

Because of logistical considerations, it was not possible to translate the portion of the questionnaire taken from the standardized respiratory questionnaire of the American Thoracic Society (Ferris, 1978) into Chinese. Furthermore, the Chinese physician administering the questionnaire did not receive the amount of interviewer training recommended by the ATS prior to administration. (Ferris, 1978). Therefore, although the ATS questionnaire is quite structured, it is not known if the physician deviated from the required format when questioning each worker. The questions relating to a symptoms that may have been due to metal fume fever were open-ended, introducing the possibility of greater bias when a history of such symptoms was elicited. Lastly, the accuracy of all of questions, when translated into Chinese, is not known.

With these caveats in mind, high rates of cough and phlegm production were observed in the workers. These symptoms may either be the result of chronic exposure to metal fumes, other dusts, or cigarette smoking. Increased rates of chronic brochitis have been frequently reported in workers in various types of foundries. However, there is disagreement as to the degree to which the chronic bronchitis can be attributed to the workplace exposures (Becklake, 1983; Morgan, 1978).

Similarly, throat irritation was noted quite frequently. Although this symptom is associated with metal fume fever, it more likely represents a non-specific irritant effect from fumes or dusts. Indeed, while thirteen of the subjects recalled at least one of the symptoms associated with metal fume fever, if the presence of fever/chills is taken into account, only three workers gave a convincing history of an illness that may have been metal fume fever.

Additional exposures to agents such as silica, polycyclic aromatic hydrocarbons and fumes of other metals with well recognized health effects may occur in foundries. The zinc ingots used in the study foundry were said to be relatively pure (> 90% zinc) and sand molds were not required for casting, making significant co-exposures to many of these agents less likely. More detailed investigations of additional exposures, apart from the multi-element analysis of the biological specimens, was beyond the scope of the study.

5.3 Personal Air Sampling

The slope of the regression line in Figure 4, showing the amount of zinc measured by atomic absorption spectrometry (AAS) plotted against the mass of the particulate sample obtained by weighing the filter, is 1.16. However, if the two samples with the highest amount zinc measured by AAS are excluded as outliers from the calculation, the slope decreases to 0.88.

AAS measures the amount of atomic zinc present whereas the zinc present in the undigested particulate sample would be expected to be present as zinc oxide. Dividing the atomic weight of zinc (65) by the molecular weight of zinc oxide (81) one derives a figure of 0.80. Therefore, these calculations suggest that the particulate sample consisted of zinc compounds, the majority of which consisted of zinc oxide. Since the slope is greater than 0.80, metallic zinc compounds may also have been present.

5.4 Serum Zinc Measurements

Part of the difficulty in interpreting zinc measurements, as well as those of most trace elements, lies in the nature of the reference range. As discussed by Guidotti et al. (1997), a distinction must be made between a reference range and a normal range. For many standard clinical tests in medicine such as blood glucose measurements, a normal range has been established. This has been derived from large systematic surveys on healthy populations. Moreover, the

study subjects are often followed into the future to rule out any pre-clinical disease that may influence the initial measurement. The distribution of results is Gaussian and the upper and lower limits of normality are set at ± 2 standard deviations with respect to the mean. Although values beyond these limits would therefore occur in 5% of healthy people, most such values, particularly if obtained from sub-populations with a high prevalence of disease such as individuals with symptoms of diabetes, suggest a derangement in homeostatic mechanisms.

In contrast, for most trace elements, including zinc, only a reference range is available. This has been established through a "convenience" sample of presumed healthy individuals rather than a systematic study. The upper and lower limits of the reference range are usually set according to the highest and lowest values observed in this group. For a reference range, the distribution of the values is not known, measurements on individuals with exposure above background levels are not included, and the relationship of this range to clinically significant or toxic levels is not known (Guidotti et al., 1997).

Attempts have been made to measure zinc, almost exclusively in serum, in cases of metal fume fever with inconsistent results (Noel and Ruthman, 1988). Most are uninterpretable since the timing of the test in relation to exposure is not given.

In the case investigated by Vogelmeier et al. (1987), in which the subject became symptomatic after two exposures, the serum zinc at an unspecified interval following each exposure was elevated (6.9 and 7.0 mg/L, equal to 690 and 700 μg/dL)[3]. In 14 welders investigated by Blanc et al. (1991), the mean serum zinc was not elevated at 6 and 20 hours post-exposure (14.8 ± 2.3 μmol/L and 11.5 ± 2.6 μmol/l)[4]. Only two of the welders in this group actually developed metal fume fever and their individual levels were not reported.

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3. In the text of the article by Vogelmeier et al. (1987) the authors refer to "the blood level of zinc". If these measurements were in fact made on whole blood, the elevation could be spurious. The methodology cited for zinc analysis is for a determination in serum and it is therefore presumed that the measurement was made on this fraction.
4. The serum values for zinc in the study by Blanc et al. (1991) were actually reported consistently in units of mmol/L. However, since the authors described these results as normal and also used these units for the upper limit of the normal range, it is presumed that this is a typographical error and that the correct units are μmol/L.

Noel and Ruthman (1988) reported serum zinc levels 12 hours after exposure in two labourers cutting galvanized steel who developed metal fume fever. They describe values of 179 µg/dL and 161 µg/dL as "elevated" compared to a "normal" range of 55 to 150 µg/dL. The upper limit of this range is usually cited for plasma whereas the sample measurements were made in serum. Since serum zinc measurements have been reported to be up to 16% higher than plasma (Abu-Hamdan et al., 1981) these results are better described as being marginally elevated or at the upper limit of the reference range.

A more likely possibility is that circulating levels of zinc decline in metal fume fever. In the first set of their bronchoalveolar lavage studies on welders with metal fume fever, Blanc et al. (1991) found a statistically significant inverse correlation between cumulative zinc exposure and serum zinc. Ulvik (1983) presented a compelling case report of a man with metal fume fever in whom serum zinc decreased. Three measurements were made during the course of his illness. Six hours after the onset of symptoms serum zinc was 11.3 µmol/L, 23 hours after the onset of symptoms: 9.5 µmol/L, and 6 days after symptom onset: 13.3 µmol/L. Ulvik (1983) noted that low serum zinc is a feature of several other inflammatory conditions as well as myocardial infarction. He speculated that the decline in serum zinc in metal fume fever may be "an unspecific (sic) response to a local inflammation in the lung tissue" (Ulvik, 1983). Ulvik proposed a sequestering of circulating zinc from plasma into the liver. Work by Leber and Miya (1976) has shown that subcutaneous injections of zinc induces the synthesis of hepatic metallothionein in mice, suggesting that metallothionein may be the agent responsible for this process.

In this study, no association was found between zinc exposure and serum zinc. Since the workers did not actually develop metal fume fever, the non-specific inflammatory mechanism proposed above was not operating to decrease serum zinc levels.

5.5 Urine Zinc Measurements

Much less information is available on measurements of zinc in urine in metal fume fever. Anthony, Zamel, and Aberman (1978) presented a case report of a welder exposed to both zinc and cadmium fumes whose clinical picture was more consistent with a toxic pneumonitis with pulmonary edema. A urine zinc on the tenth hospital day was 400 mg/L. The authors do not specify whether this measurement was made on a single void specimen or 24 hour collection.

Armstrong et al. (1983) investigated an outbreak of metal fume fever in 26 workers cutting brass pipes with carbon-air torches. The outbreak was ascribed to copper since the piping was found to consist of 90% copper and 10% nickel with only "trace" amounts of zinc and markedly elevated urinary copper levels were measured in single void samples in five of twelve workers. Urinary zinc was also modestly elevated, with a reported range of 0.05 to 1.8 mg/L (Armstrong et al., 1983).

A very recent study by Pasker et al. (1997) included zinc measurements from end of shift urine samples. Although actual values were not reported, small, but statistically significant higher levels were found in exposed workers compared to unexposed (Pasker et al., 1997).

In the present study, a statistically significant association between mean air exposure to zinc and the amount of zinc measured in cross shift urine collections was found ($p=0.04$, $rho=0.47$). Although this association was largely driven by the afternoon shift air sampling values ($p=0.02$, $rho=0.55$), the association with the morning shift values did approach conventional statistical significance ($p=0.09$, $rho=0.41$). Although the blank urine samples showed acceptably low levels of zinc, it remains possible that the urine specimens could have been contaminated from the workers' clothing. The workers did not change or shower prior to voiding. However, in the study by Pasker et al. (1997), such precautions were taken to avoid contamination, and a small, but statistically significant, elevation was noted in exposed workers. The levels of urinary zinc measured by these investigators were not reported.

If this association is real, inhaled zinc oxide must be taken up from the lungs by the circulation and cleared through the kidneys very rapidly. Studies in rats have indicated that zinc oxide is cleared from the lung with an estimated half-life of 14 hours following intratracheal instillation (Hirano et al., 1989). No estimates of the half-life of zinc in circulation could be identified. It is possible that inhaled zinc, if taken up by the circulation, may be present in a labile form that is amenable to rapid renal clearance. In any event, such rapid clearance was also suggested by the study by Pasker et al. (1997), in which the relative elevation in urinary zinc levels was noted in end of shift samples.

As most of the workers had completed shifts 16 to 24 hours prior the study shift, the urinary zinc measurements may actually reflect exposure prior to the start of the study. Furthermore, variations in urine output may not have been adequately accounted for in this study. Therefore, an attempt to confirm these findings should be performed on workers without recent exposure to zinc and include 24 hour urine collections and/or measurements of urine creatinine. In the present study, after analysis of the urine specimens for zinc and other elements, insufficient sample remained for a creatinine determination.

Since serum appears to be a poor choice of substrate for establishing inhalational exposure to zinc, future studies and case reports of metal fume fever should include measurements of zinc in urine.

5.6 Blood Indices

The relationship between zinc exposure and several of the blood indices was examined. Scatter plots of hemoglobin, total white blood cell count, percent neutrophils and percent lymphocytes against mean air zinc exposure are depicted in Figures 7 to 10.

Statistical analysis of the relationship between mean air zinc exposure and blood indices revealed several trends. Zinc exposure was related to increased percentage neutrophils ($p=0.003$, $r=0.64$), consistent with observations from studies of metal fume fever. However, zinc exposure was related to decreased

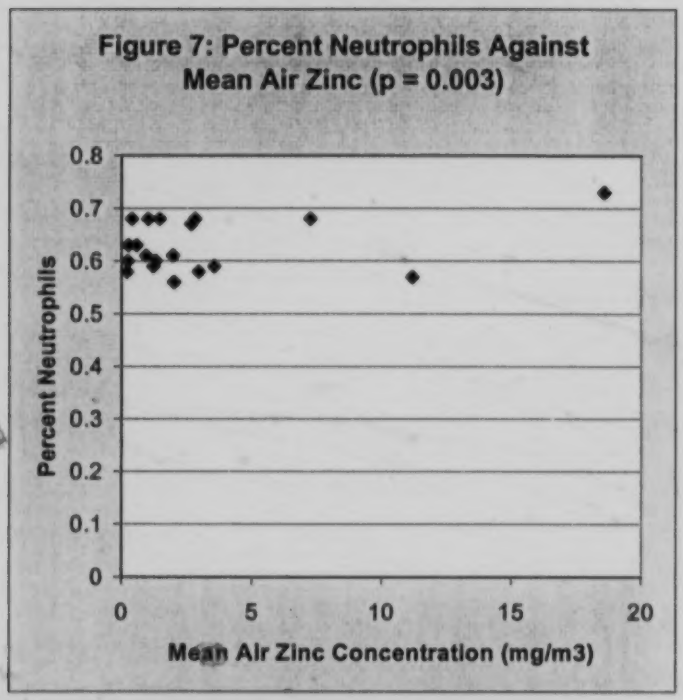
Figure 7: Percent Neutrophils Against Mean Air Zinc (p = 0.003)
Percent Neutrophils
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
Mean Air Zinc Concentration (mg/m3)

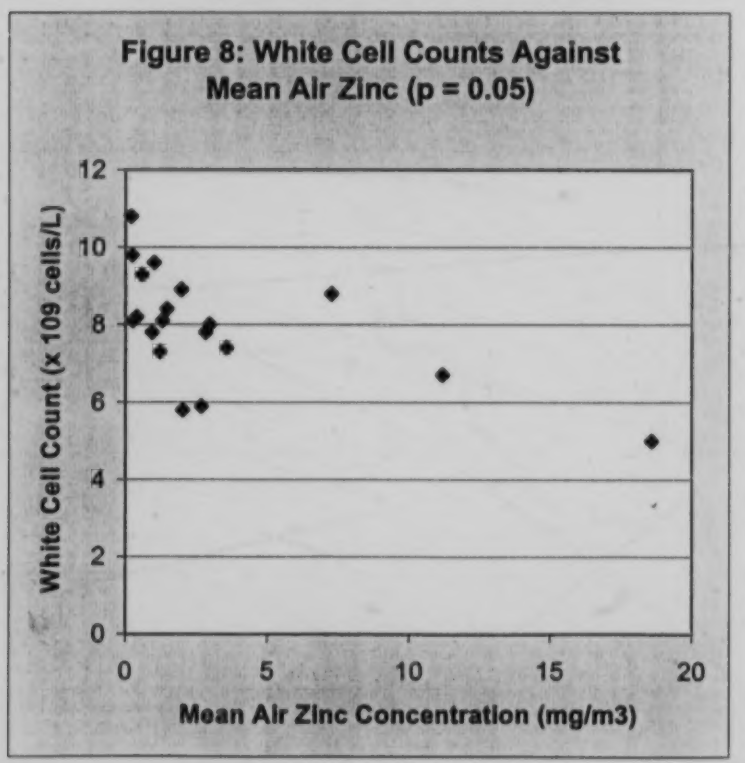
Figure 8: White Cell Counts Against Mean Air Zinc (p = 0.05)
White Cell Count (x 109 cells/L)
12
10
8
6
4
2
0
0
5
10
15
20
Mean Air Zinc Concentration (mg/m3)

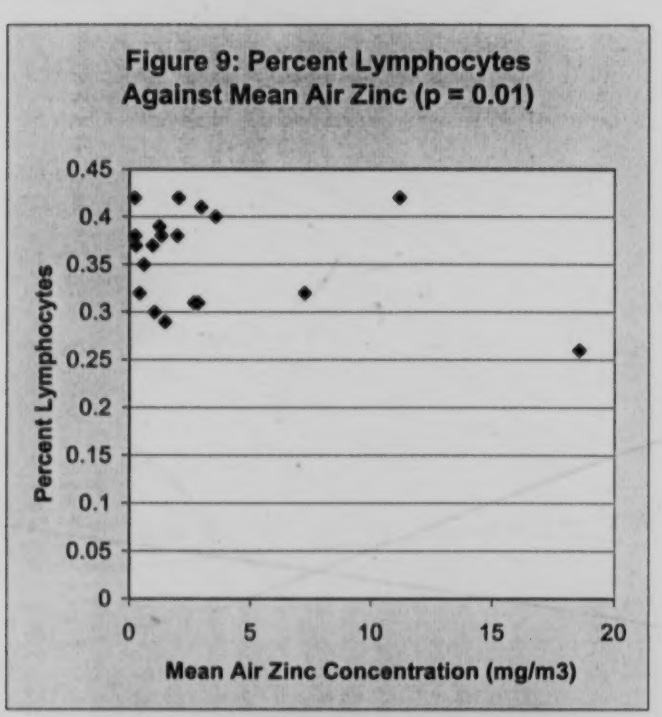
Figure 9: Percent Lymphocytes Against Mean Air Zinc (p = 0.01)
Percent Lymphocytes
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
5
10
15
20
Mean Air Zinc Concentration (mg/m3)

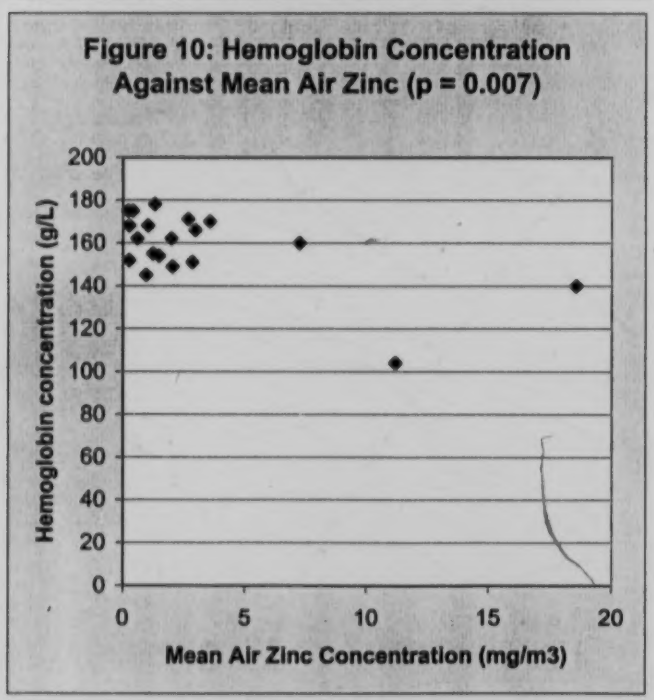
Figure 10: Hemoglobin Concentration Against Mean Air Zinc (p = 0.007)
Hemoglobin concentration (g/L)
200
180
160
140
120
100
80
60
40
20
0
0
5
10
15
20
Mean Air Zinc Concentration (mg/m3)

total white cell counts, although this association was of borderline statistical significance (p=0.05, r=0.45). Zinc exposure was also related to a decrease in percentage lymphocytes (p=0.01, r=0.56). Therefore, zinc exposure is not related to an absolute increase in neutrophils. The observed association between zinc exposure and increased percentage neutrophils reflects a decrease in total white cell count with a further, disproportionate decrease in lymphocytes.

Zinc exposure was associated with decreased hemoglobin (p=0.007, r=0.59). Since zinc exposure is not known to cause decreases in hemoglobin or white cell counts, the observation of such an association suggests effects from possible co-exposures. Several additional elements were therefore measured in serum, urine, and whole blood using ICP-MS and compared to the blood indices to explore this possibility (Table 17).

The whole blood sample was not collected in the required trace element free container. Therefore blanks were used which consisted of distilled water drawn into the same type of Vacutainer. Analysis of the blanks showed low levels of lead near the detection limit in two of three samples. Several drops of blood were removed from the whole blood samples in Baiyin for the white cell count, representing another possible source of contamination not accounted for by the blanks used.

A forward linear regression model was used to examine the contribution of urinary arsenic, blood cadmium, and blood lead to hemoglobin measurement and total white cell count. No statistical significant contribution to hemoglobin concentration was found for any of these three elements.

5.7 Pulmonary Involvement

Pulmonary function testing in cases of metal fume fever has revealed patterns of obstruction, restriction or both. No changes in FEV1 or FVC were seen in the twenty study subjects, consistent with a lack of symptomatology. Mean values for FEV1 and FVC increased with each successive assessment. A

Table 17: Measurements of Blood Cadmium, Blood Lead and Urinary Arsenic

Cadmium (ug/L)	Cadmium (mmol/L)	Lead (ug/L)	Lead (umol/L)	Arsenic (ug/L)	Arsenic (umol/L)
1.28	11	172	0.83	52	0.69
0.84	7	188	0.91	42	0.56
1.22	11	190	0.92	20	0.27
4.80	43	206	0.99	48	0.64
4.23	38	204	0.98	50	0.67
9.60	85	192	0.93	30	0.40
7.70	69	220	1.06	n.d.	n.d.
0.98	9	164	0.79	127	1.70
10.80	96	345	1.67	79	1.05
6.66	59	187	0.90	39	0.52
5.98	53	118	0.57	59	0.79
7.47	66	230	1.11	42	0.56
1.37	12	216	1.04	164	2.19
3.32	30	185	0.89	30	0.40
2.92	26	181	0.87	85	1.13
5.78	51	181	0.87	20	0.27
9.00	80	194	0.94	45	0.60
0.70	6	245	1.18	38	0.51
2.20	20	176	0.85	32	0.43
6.84	61	199	0.96	103	1.38

n.d. – Below method detection limit of 1 μg/L.

circadian variation in FEV1 has been described in shift workers, which may account for the observed increase. Guberan et al. (1969) noted a 4.1% increase in FEV1 comparing pre- and post-shift measurements at 6 AM and 2 PM. A smaller effect was seen for the FVC, which increased by 1.2%.

Alternatively, the increase observed in the present study may reflect an improved understanding and effort on the part of the workers as familiarity with the forced exhalation maneuver increased. The mean FEV1 and FVC from the measurements made 24 hours post-shift showed a marginal increase from those made immediately post-shift even though both measurements were taken at the same time of day.

The patterns of mild obstruction noted in subjects 4 and 6 may be chronic effects possibly from cigarette smoking, rather than acute changes. Evidence of obstruction was noted consistently at each assessment. Moreover, subject 4 was the oldest participant in the study (44 years) and had a five pack year history of smoking. Subject 6 had a seven pack year history and also reported a five year history of cough with phlegm production in addition to a history of wheezing.

It remains possible that changes may have been missed since no control group was included. In this case, both groups may have been noted to have increased measurements for FEV1 and FVC with successive assessments but the unexposed group may have shown a relatively greater increase. Pasker et al. (1997) performed such a study using spirometry on 57 workers exposed to an electrical furnace in a steel recycling plant generating high levels of zinc oxide and 55 unexposed workers from other areas of the plant. No statistically significant differences in pulmonary function measured was found between exposed and unexposed workers during the day shift. However, for those working the night shift, the authors reported statistically significant declines between exposed and unexposed workers. For the workers on the night shift, FVC declined by an average of 99 ± 178 ml and FEV1 by 140 ± 140 ml.

Although the authors report a statistically significant difference, the standard error of the difference for both measurements is as large or larger than the value of the difference itself. In view of the small magnitude of the difference,

a larger sample size is clearly needed to obtain more precise estimates. It is unclear why a difference would be seen at night but not during the day. Pasker et al. (1997) speculate that the workplace exposure may heighten the physiological decline in FVC and FEV1 at night.

Therefore, two broad issues remain to be addressed with respect to the functional changes, as well as radiographic changes, following exposure to zinc oxide. In cases of overt illness (metal fume fever) the frequency, nature and timing of the changes remain to be clarified. This may prove difficult to accomplish in studies of occupational cohorts because of both tachyphylaxis and longer term tolerance. Controlled exposure studies are a promising alternative. Those studies to date have not adequately addressed this question since pulmonary function studies and chest radiographs on sufficient numbers of subjects who clearly develop metal fume fever have not been performed.

The second outstanding issue relates to more subtle effects from low level exposure without the manifestations of metal fume fever. This type of study could only be performed on an occupational cohort since a large sample would be required to detect what may only be small effect with confidence.

6. CONCLUSION AND IDENTIFICATION OF FUTURE RESEARCH NEEDS

When considered collectively with other inhalation fevers, metal fume fever represents a substantial source of morbidity among workers in a variety of settings. Moreover, with recent evidence emerging from experimental studies of metal fume fever which indicates that a long term tolerance may be operative, the similarities between these conditions increase. Such striking similarities point to a common pathway, in which widely different chemical agents initiate the same cascade of cytokine activation. Elucidating this common pathway would provide a great deal of insight into a poorly understood pulmonary response mechanism.

With respect to the well known short term tolerance (tachyphylaxis) acquired in metal fume fever, a role for metallothionein is implicated by the concordance between the chronology of the induction of this protein in response to zinc exposure and the time required to gain or lose tachyphylaxis. Although some suggestive evidence is available from animal studies using zinc, metallothionein has not been considered in the setting of other inhalation fevers, such as organic dust toxic syndrome.

In spite of being a very common condition, many features of metal fume fever have not been well characterized. These can be subdivided into clinical features and features related to exposure assessment to zinc.

In terms of clinical features, although numerous case reports indicate that transient functional and radiographic changes occur in metal fume fever, there has never been a systematic attempt to investigate these changes in a large cohort of cases. In the present investigation, no cases were observed despite sufficient exposures in several subjects, probably as a result of a combination of both tachyphylaxis and longer term tolerance. Characterizing these changes is essential to allow the clinician to distinguish metal fume fever from a potentially life-threatening toxic pneumonitis.

The failure to observe cases in this cohort indicates that controlled exposures in volunteers may be a more feasible method to prospectively investigate these changes. Such exposures have been performed quite

successfully by several investigators, but to date, have not included functional and radiographic investigations upon large numbers of individuals who develop metal fume fever. Based on case reports, the radiographic and functional changes appear to occur at about 12 hours after exposure, which therefore represents a crucial window for the timing of such investigations.

Finally, most case reports and investigations of metal fume fever have attempted to assess exposure through measurements of zinc in serum. A careful review of these studies, together with the results of this investigation, strongly suggest that serum zinc is a poor indicator of the level of exposure to inhaled zinc. However, a statistically significant association between urine zinc and exposure to zinc was observed in the study subjects. A similar result has been noted in at least one other recent study (Pasker et al., 1997).

In view of the sample size of 20, this finding needs to be confirmed through studies on larger numbers of subjects, ideally with a wide range of exposures. This type of study could be performed on a large occupational cohort, since the actual development of metal fume fever would not be required. Any such study should account for previous recent zinc exposures and include urine creatinine measurements to correct for variations in urine output.

The results further suggest that inhaled zinc is taken up into the circulation and subsequently cleared by the kidneys quite rapidly. Whatever zinc is present in the circulation from inhalation is therefore quite labile and may be in a form distinct from other zinc complexes. If so, speciation studies to identify specific chemical forms of zinc in this setting may be more helpful than total measurements.

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APPENDIX 1: INFORMATION SHEET FOR STUDY PARTICIPANTS

A Systematic Investigation of Metal Fume Fever

Principal Investigator: X. Chris Le, PhD

Co-Investigators: Christopher J. Martin, MD
Tee L. Guidotti, MD, MPH
Chaoke Liang
Baoshan Yuan

Background

You are being asked to participate in a medical study of an illness called metal fume fever.

Metal fume fever has symptoms that are very similar to influenza (fever, chills, muscle aches) and is caused by inhaling zinc fumes. These symptoms usually develop several hours after inhaling these fumes and disappear after 1 to 2 days. No medical treatment is necessary. All cases of metal fume fever have made a complete recovery and there appear to be no long term effects. Through your work in the foundry you may be exposed to zinc fumes and may have already experienced this illness.

Purpose

We wish to study the changes that can occur in someone who has metal fume fever in three areas:

1. Changes in chest X-rays
2. Changes in lung function
3. Changes in levels of zinc in blood and urine

Procedures

If you agree to take part in the study, we ask that you try to carry out your normal work duties as much as you can. The study will involve 6 to 7 visits with us over the next 2 days, including this visit. This first visit will take 30-45 minutes, the other visits should not take longer than 20-25 minutes.

During the visits, you will be interviewed and examined by a physician, have your temperature measured, have a chest X-ray, and have your lung function measured by a machine. We will take one blood sample (2 tubes, each 2-5 ml / 2-3 teaspoons) from you. We also ask that you collect all the urine you produce during your shift in a container we will give you.

After this visit, other visits will occur 1 hour after you have started work, 6 hours after you have started work and after your shift is completed. We will then examine you again 16 hours after you start work and 24 hours after you started work. We may ask you to return for one final visit 48 hours after you started work.

If you develop symptoms of metal fume fever, we ask that you stop working until your symptoms have resolved.

Possible Benefits

It is important to understand what changes in your body occur in metal fume fever in order to correctly diagnose this illness and recognize the differences between metal fume fever and other diseases that can have very similar symptoms. Also, by studying this disease, we hope to draw attention to metal fume fever and encourage people to try to prevent it from occurring.

Possible Risks

Taking the blood sample may cause some minor bruising. Breathing very hard into the machine may rarely cause some people to faint. We will take 5 to 6 chest X-ray pictures in total. The radiation you are exposed to from this is very low.

Confidentiality

Personal records relating to this study will be kept confidential. Although we will share the results of the study with any interested party, including your employer, only the investigators will have records that identify you by name.

You will not suffer lost wages for time away from work because of this study.

You are free to withdraw from the research study at any time, and your medical care and employment status will not be affected in any way.

Please contact any of the individuals below if you have any questions or concerns:

X. Chris Le

Boashan Yuan

APPENDIX 2: QUESTIONNAIRE
METAL FUME FEVER STUDY

Date: _____ **Time:** _____

Name: _____ _____
Last Name First Name

Sex: ☐ Male ☐ Female

Date of Birth: _____ _____ _____
Day Month Year

Job Title / Duties: _____

_____

_____

Length of time employed with the Baiyin Corporation Foundry?

From: _____ _____ To: _____ _____
Month Year Month Year

Metal Fume Fever History

Have you ever had attacks of fever and chills in relation to your work that do not seem to be caused by a common cold or influenza?

List Symptoms: _____

_____

How long do these attacks last? _____

_____

When, in relation to work, did the symptoms begin? _____

_____

How many such attacks have you experienced? _____

_____

RESPIRATORY HISTORY:

1. Cough:

A. Do you usually have a cough? (Count a cough with first smoke or on first going out of doors. Exclude clearing of throat.) ☐ Yes ☐ No

[IF NO, SKIP TO QUESTION 1C.]

B. Do you usually cough as much as: 4 to 6 times a day, 4 or more days out of the week? ☐ Yes ☐ No

C. Do you usually cough at all on getting up, or first thing in the morning? ☐ Yes ☐ No

D. Do you usually cough at all during the rest of the day or at night? ☐ Yes ☐ No

[IF YES TO ANY OF THE ABOVE 1. A,B,C OR D), ANSWER THE FOLLOWING:]
[IF NO TO ALL, CHECK DOES NOT APPLY AND SKIP TO QUESTION 2.]

E. Do you usually have a cough like this on most days for 3 consecutive months or more during the year? ☐ Yes ☐ No
Does not apply _____

F. For how many years have you had this cough? _____
Number of years
Does not apply _____

2. Phlegm:

A. Do you usually bring up phlegm from your chest? (Count phlegm with the first smoke or on first going out of doors. Exclude phlegm from the nose. Count swallowed phlegm.) ☐ Yes ☐ No

[IF NO, SKIP TO 2C.]

B. Do you usually bring up phlegm like this as much as twice a day, 4 or more days out of the week? ☐ Yes ☐ No

C. Do you usually bring up phlegm at all on getting up, or first thing in the morning? ☐ Yes ☐ No

D. Do you usually bring up phlegm at all during the rest of the day or at night? ☐ Yes ☐ No

[IF YES TO ANY OF (2.A-B-C-D), ANSWER THE FOLLOWING:]
[IF <u>NO TO ALL</u>, CHECK DOES NOT APPLY AND SKIP TO QUESTION 3.]

E. Do you bring up phlegm like this on most days for 3 consecutive months or more during the year? ☐ Yes ☐ No

F. For how many years have you had trouble with phlegm? _____ ☐ N/A
Number of Years

3. Episodes of Cough and Phlegm:

A. Have you had periods or episodes of increased*) cough and phlegm lasting for 3 weeks or more each year? ☐ Yes ☐ No
***(For persons who usually have cough and/or phlegm)**

[IF YES TO 3. A, ANSWER B]

B. For how long have you had at least 1 such episode per year? _____ ☐ N/A
Number of Years

4. Wheezing:

A. Does your chest ever sound wheezy or whistling:
1. When you have a cold? ☐ Yes ☐ No
2. Occasionally apart from colds? ☐ Yes ☐ No
3. Most days or nights? ☐ Yes ☐ No

[IF YES TO QUESTION IN 4.A (1,2,3) ABOVE ANSWER B]

B. For how many years has this been present? _____ ☐ N/A
Number of Years

C. Have you ever had an attack of wheezing that has made you feel short of breath? ☐ Yes ☐ No

[IF YES TO QUESTION 4.C answer D,E and F]

D. How old were you when you had your first such attack? _____ Age in years ☐ N/A

E. Have you had 2 or more such episodes? ☐Yes ☐ No ☐ N/A

F. Have you ever required medicine or treatment for the(se) attack(s)? ☐Yes ☐ No ☐ N/A

5. Chest Colds and Chest Illness:

A. If you get a cold, does it <u>usually</u> go to your chest? (Usually means more than ½ the time) ☐ Yes ☐ No
Don't get colds _____

B. During the past 3 years, have you had any chest illness that have kept you off work, indoors at home, or in bed? ☐ Yes ☐ No

[IF YES TO 5A ANSWER C AND D.]

C. Did you produce phlegm with any of these chest illnesses? ☐ Yes ☐ No
Does not apply _____

D. In the last 3 years, how many such illnesses, with (increased) phlegm, did you have which lasted a week or more?
___ Number of illnesses
___ No such illnesses
Does not apply _____

6. Past Illnesses:

A. Did you have any lung trouble before the age of 16? ☐ Yes ☐ No

B. Have you ever had any of the following:

7.A. Attacks of bronchitis? ☐ Yes ☐ No

[IF YES TO A Bronchitis answer B and C.]

B. Was it confirmed by a doctor? ☐ Yes ☐ No
Does not apply _____

C. At what age was your first attack?
_____ Age in years
Does not apply _____

8.A. Pneumonia (include bronchopneumonia)? ☐ Yes ☐ No

[IF YES TO A Pneumonia answer B AND C]

B. Was it confirmed by a doctor? ☐ Yes ☐ No
Does not apply _____

C. At what age did you first have it?
_____ Age in years
Does not apply _____

9.A. Hay Fever? ☐ Yes ☐ No

[IF YES TO A. Hay Fever answer B and C.]

B. Was it confirmed by a doctor? ☐ Yes ☐ No
Does not apply _____

C. At what age did it start?
_____ Age in years
Does not apply _____

10.A. Have You Ever Had Chronic Bronchitis? ☐ Yes ☐ No
[IF YES TO A answer B,C AND D.]

B.	Do you still have it?	☐ Yes ☐ No Does not apply _____
C.	Was it confirmed by a doctor?	☐ Yes ☐ No Does not apply _____
D.	At what age did it start?	_____ Age in years Does not apply _____

11.A. Have You Ever Had Emphysema? ☐ Yes ☐ No
[IF YES TO A answer B,C, AND D.]

B.	Do you still have it?	☐ Yes ☐ No Does not apply _____
C.	Was it confirmed by a doctor?	☐ Yes ☐ No Does not apply _____
D.	At what age did it start?	_____ Age in years Does not apply _____

12.A. Have You Ever Had Asthma? ☐ Yes ☐ No
[IF YES TO A answer B,C AND D.]

B.	Do you still have it?	☐ Yes ☐ No Does not apply _____
C.	Was it confirmed by a doctor?	☐ Yes ☐ No Does not apply _____
D.	At what age did it start?	_____ Age in years Does not apply _____

13. HAVE YOU EVER HAD:

A. Any other chest illness? ☐ Yes ☐ No
If yes, please specify _____

B. Any chest operations? ☐ Yes ☐ No
If yes, please specify _____

C. Any chest injuries? ☐ Yes ☐ No
If yes, please specify _____

14. TOBACCO SMOKING:

A. Have you ever smoked cigarettes? (No means less than 20 packs of cigarettes or 12 oz of tobacco in a lifetime or less than 1 cigarette a day for 1 year. ☐ Yes ☐ No

[IF YES TO 15. A ANSWER B.C,D,E,F AND G.]

B. Do you now smoke cigarettes (as of 1 month ago)? ☐ Yes ☐ No
Does not apply _____

C. How old were you when you first started Regular cigarette smoking? _____ Age in years
Does not apply _____

D. If you have stopped smoking cigarettes Completely, how old were you when you stopped? _____ Age stopped
Check if still smoking _____
Does not apply _____

E. How many cigarettes do you smoke per day now? ____ cigarettes per day
Does not apply _____

F. On the average of the entire time you smoked, how many cigarettes did you smoke per day? ____ cigarettes per day
Does not apply _____

G. Do or did you inhale the cigarette smoke? ☐ Yes ☐ No

Are you on any medications?

Physical Examination

Height (cm) Weight (kg)

Temperature (°C) Respiratory Rate

Respiratory Exam

Crackles: ☐ No ☐ Yes Location:

Wheezes: ☐ No ☐ Yes Location:

Other Abnormalities:

Other Systems

Other relevant abnormalities:

EXAM AT X HOURS

Work duties performed since baseline exam:

Symptoms (Check if present and state for how long)

Respiratory:
- Shortness of breath
- Wheeziness
- Cough — If yes, productive
- Throat irritation
- Chest tightness

Others: Sweet or metallic taste in the mouth
- Muscle aches
- Nausea
- Headache
- Fever
- Chills
- Rigors (Shakes)

Other (specify)

Physical Exam

Temperature (°C) Respiratory Rate

Crackles Location

Wheezes Location

Other Abnormalities: